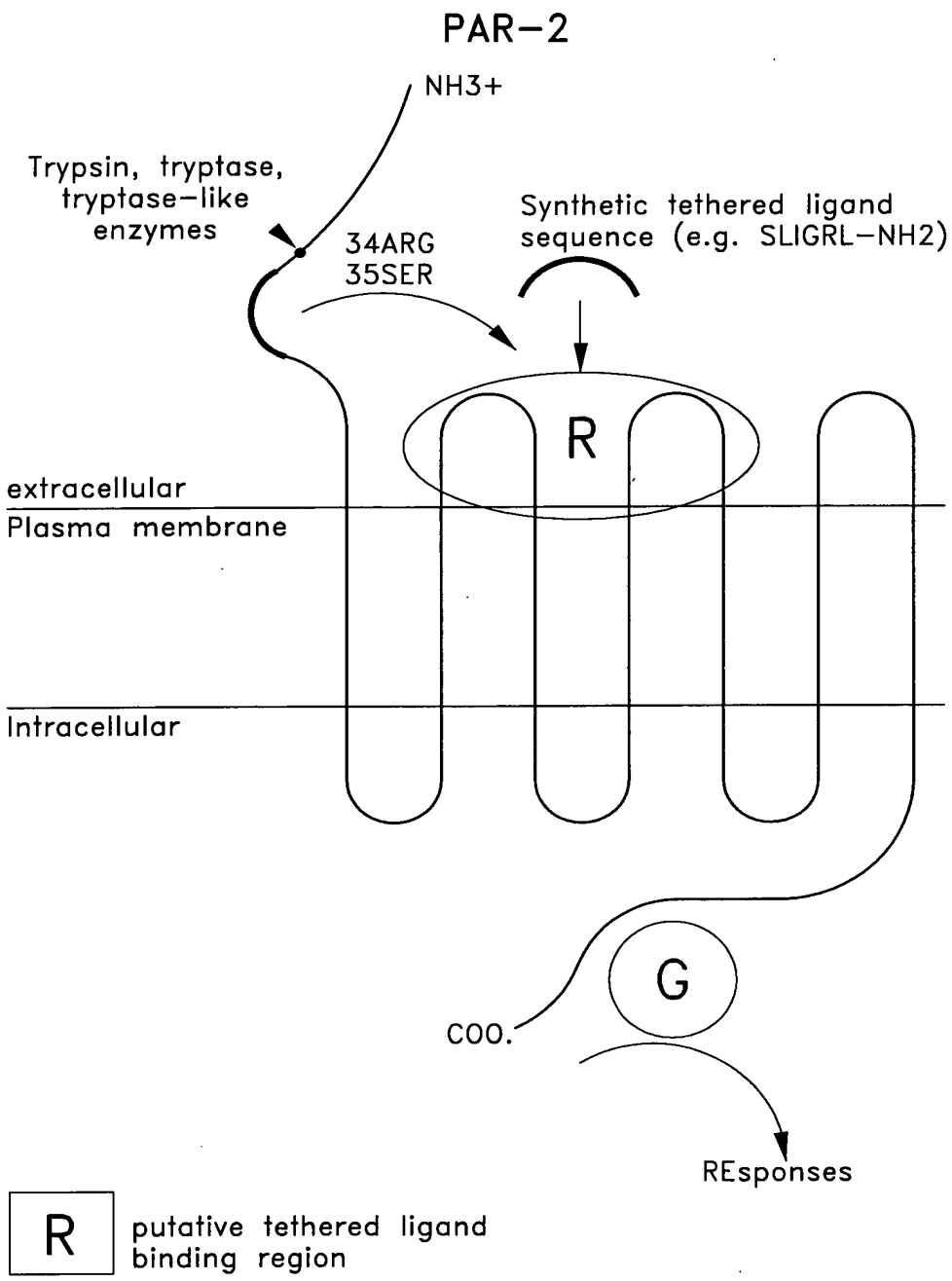


FIG. 1

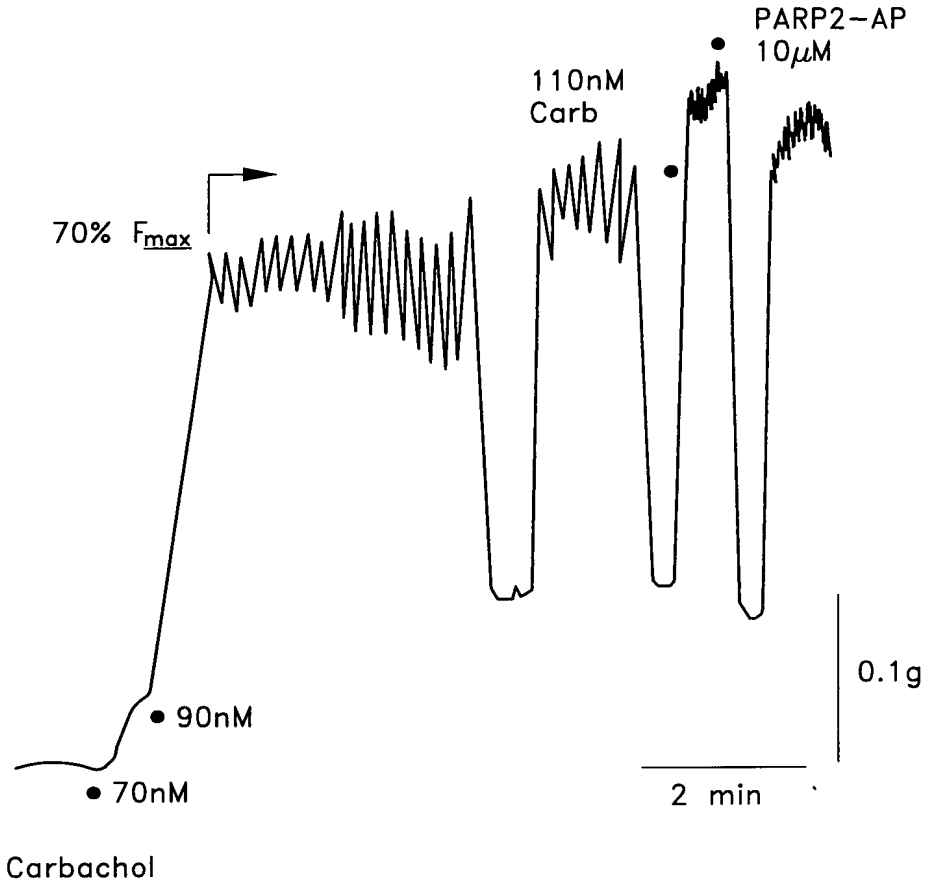

Mouse bronchi
PARP2–AP
10μM
110nM
Carb
70% Fmax
0.1g
90nM
70nM
2 min
Carbachol

FIG. 2

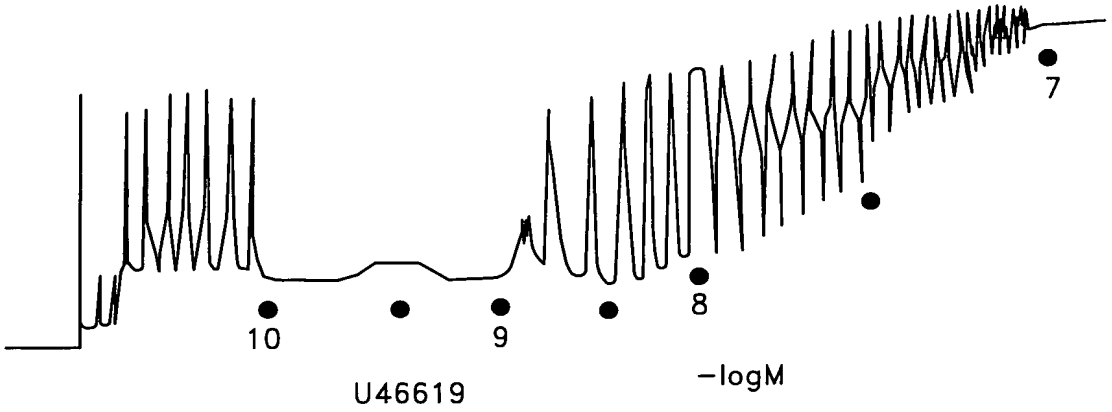


FIG. 3A

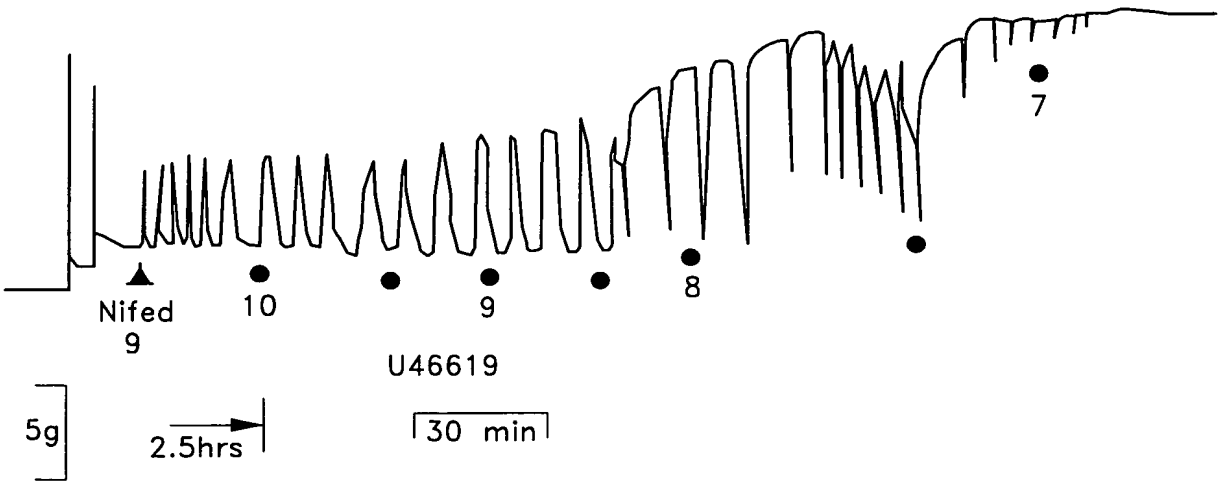


FIG. 3B

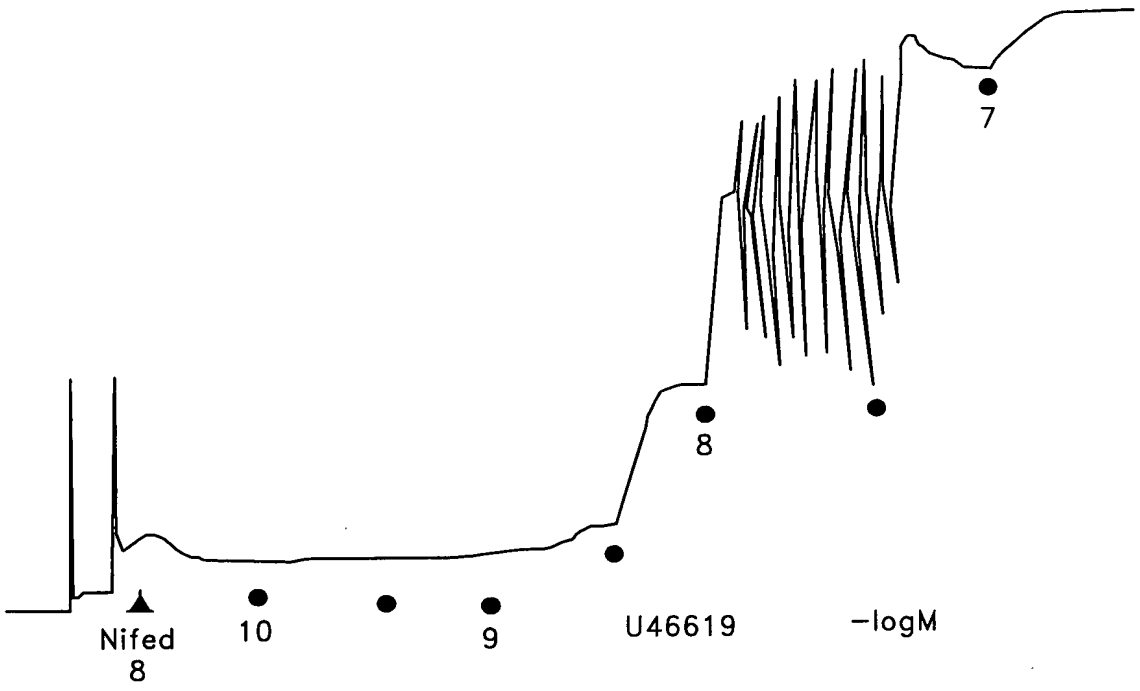


FIG. 3C

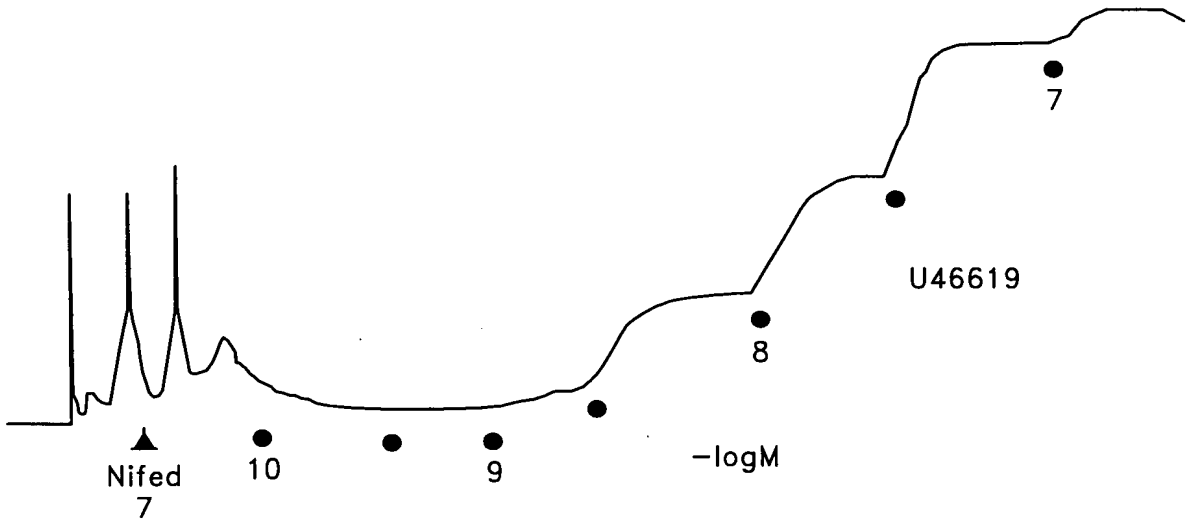


FIG. 3D

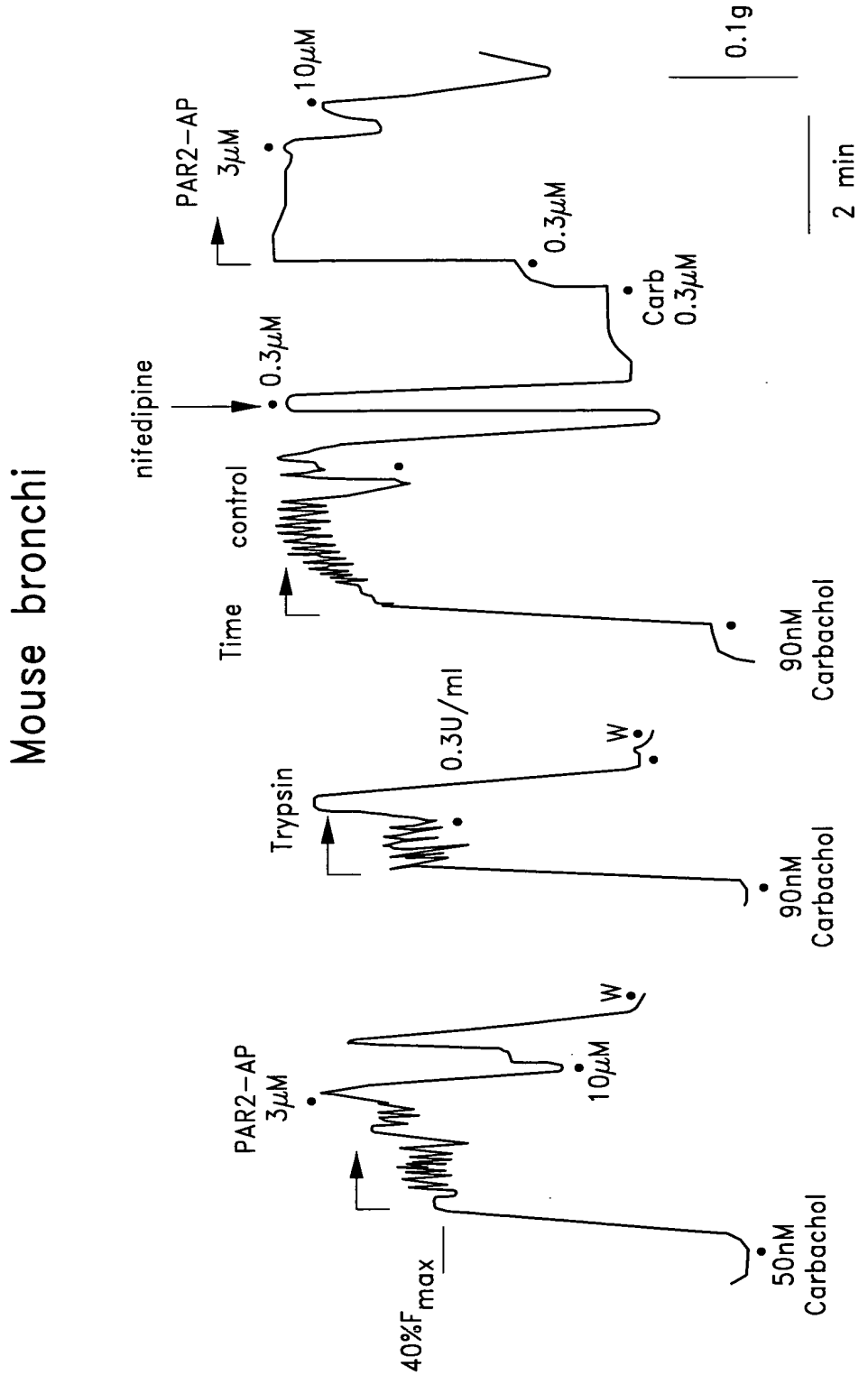

Mouse bronchi
40%F max
50nM Carbachol
PAR2-AP 3μM
10μM
W
Trypsin
0.3U/ml
W
90nM Carbachol
Time control
nifedipine
0.3μM
PAR2-AP 3μM
10μM
0.3μM
Carb 0.3μM
90nM Carbachol
0.1g
2 min

FIG. 4

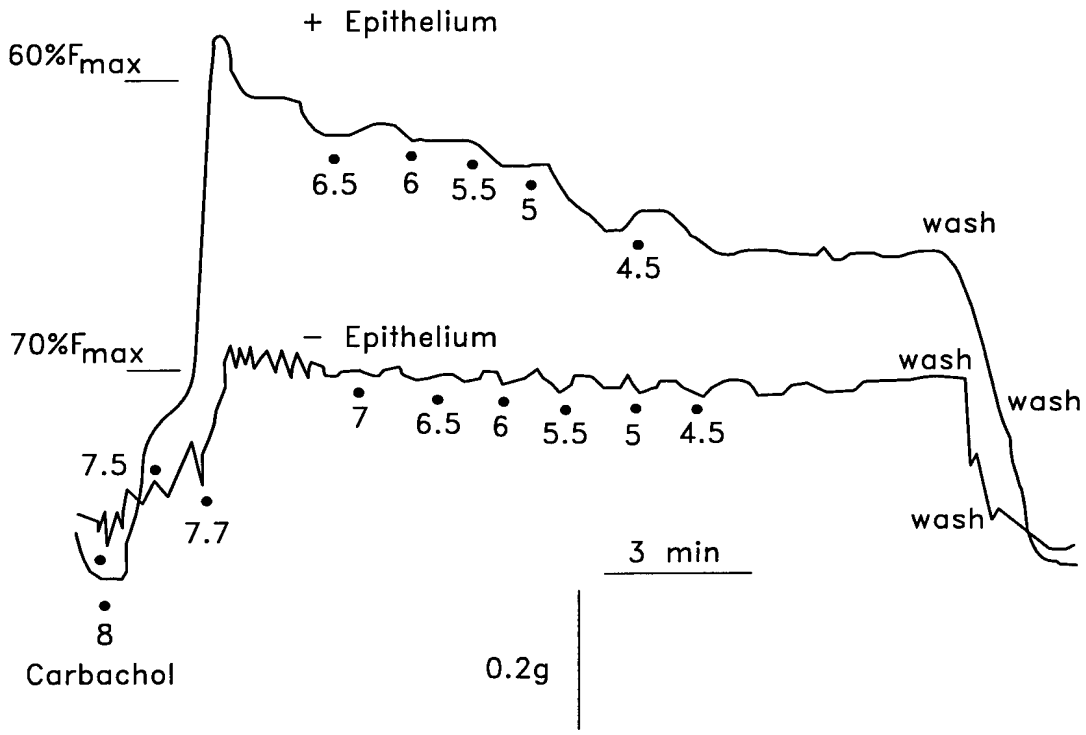

Guinea–pig trachea
+ Epithelium
60%Fmax
6.5
6
5.5
5
4.5
wash
70%Fmax
– Epithelium
wash
wash
7
6.5
6
5.5
5
4.5
7.5
7.7
wash
3 min
8
Carbachol
0.2g

FIG. 5A

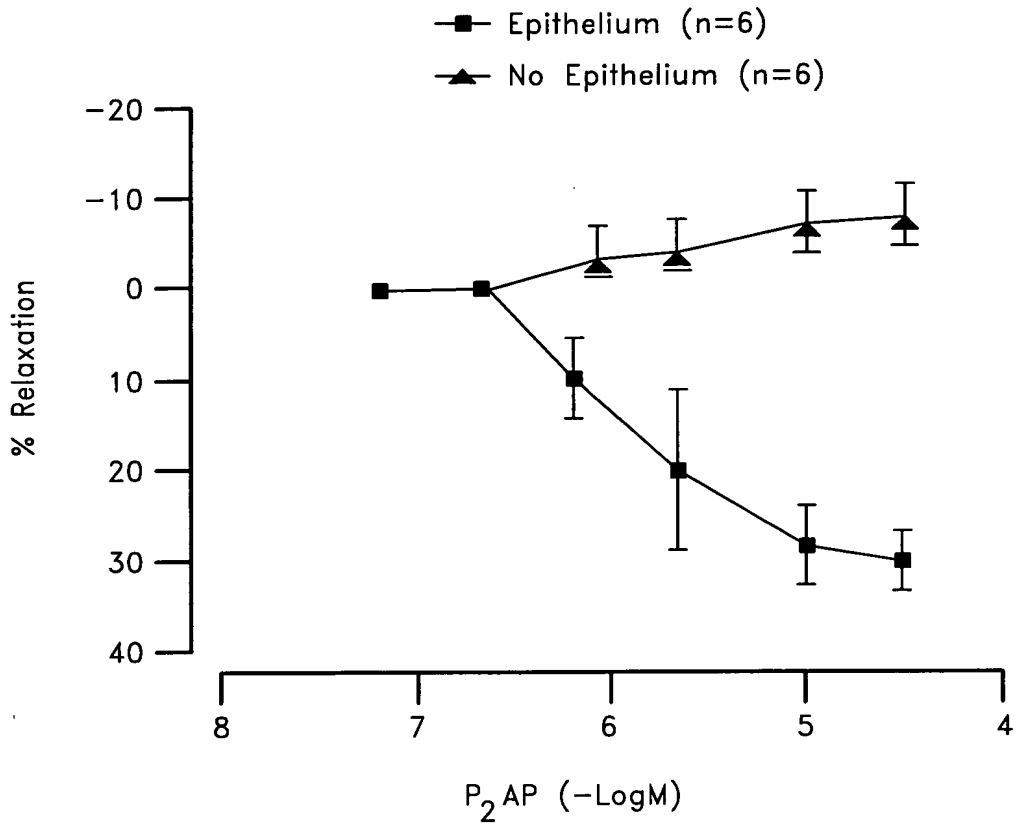

Epithelium (n=6)
No Epithelium (n=6)
% Relaxation
−20
−10
0
10
20
30
40
8
7
6
5
4
P2 AP (−LogM)

FIG. 5B

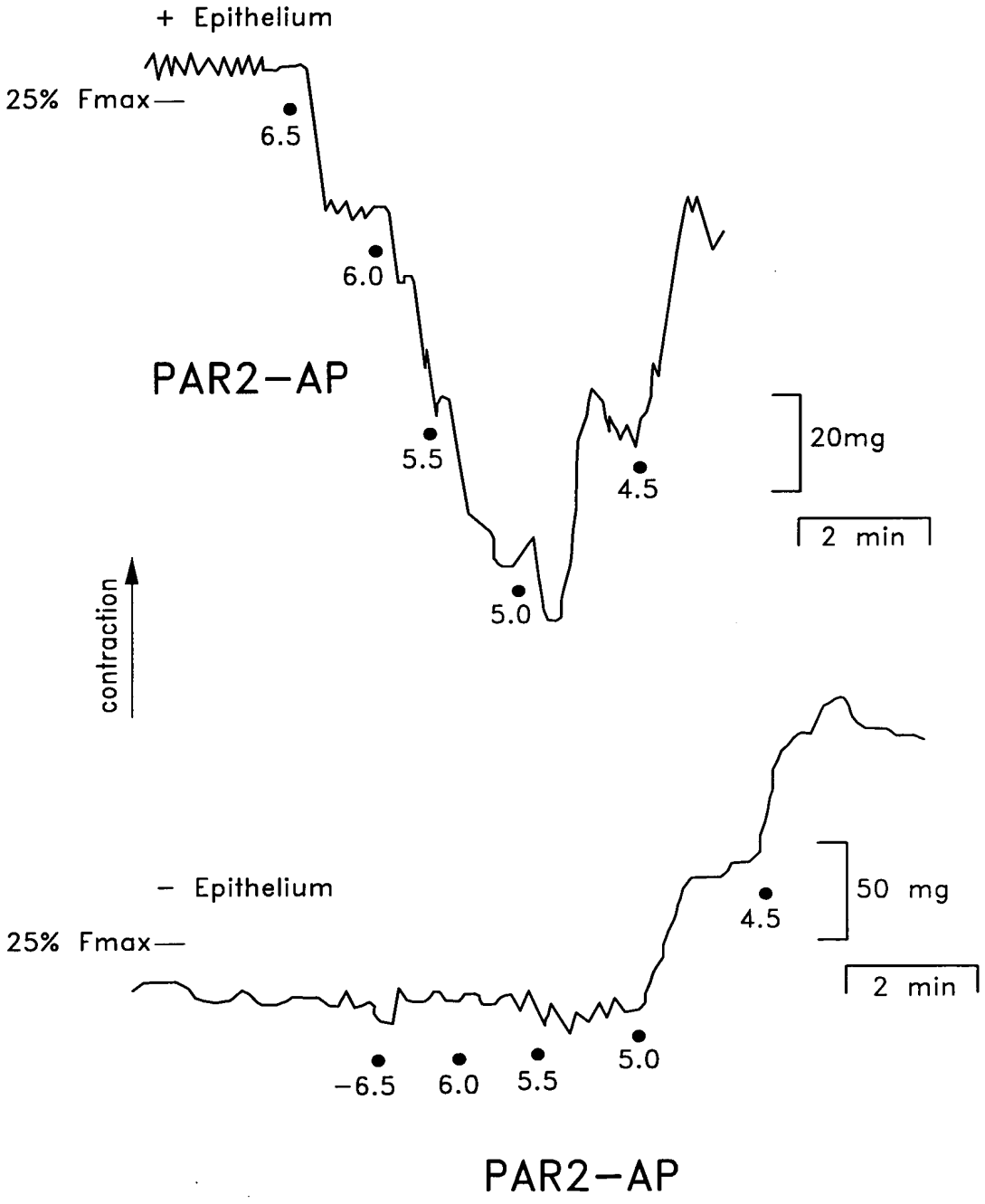

Guinea–pig Trachea
+ Epithelium
25% Fmax
6.5
6.0
PAR2–AP
5.5
5.0
4.5
20mg
2 min
contraction
– Epithelium
25% Fmax
4.5
50 mg
2 min
5.0
–6.5
6.0
5.5
PAR2–AP

FIG. 6

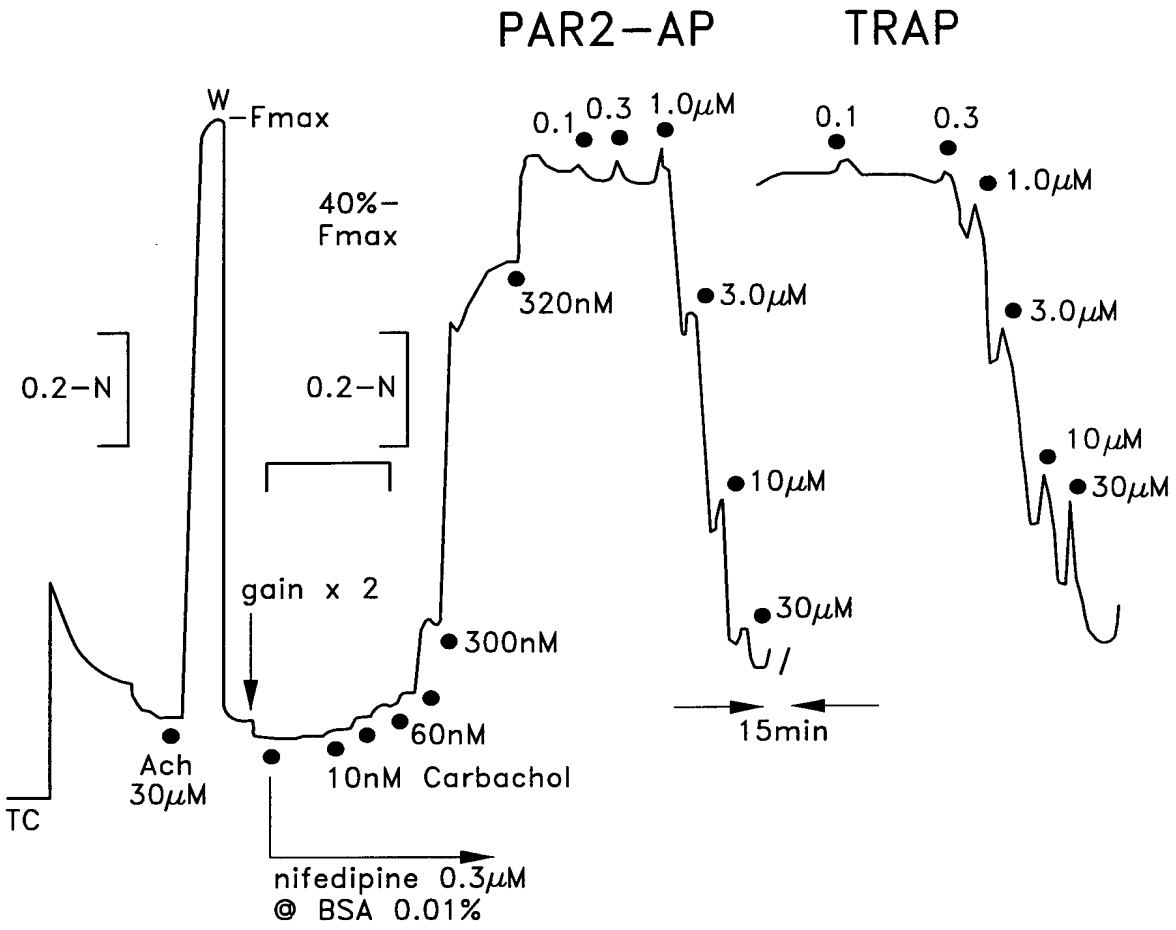

PAR2–AP
TRAP
W
–Fmax
40%–
Fmax
0.2–N
0.2–N
gain x 2
TC
Ach
30μM
0.1
0.3
1.0μM
320nM
3.0μM
10μM
30μM
300nM
60nM
10nM Carbachol
nifedipine 0.3μM
@ BSA 0.01%
15min
0.1
0.3
1.0μM
3.0μM
10μM
30μM

FIG. 7

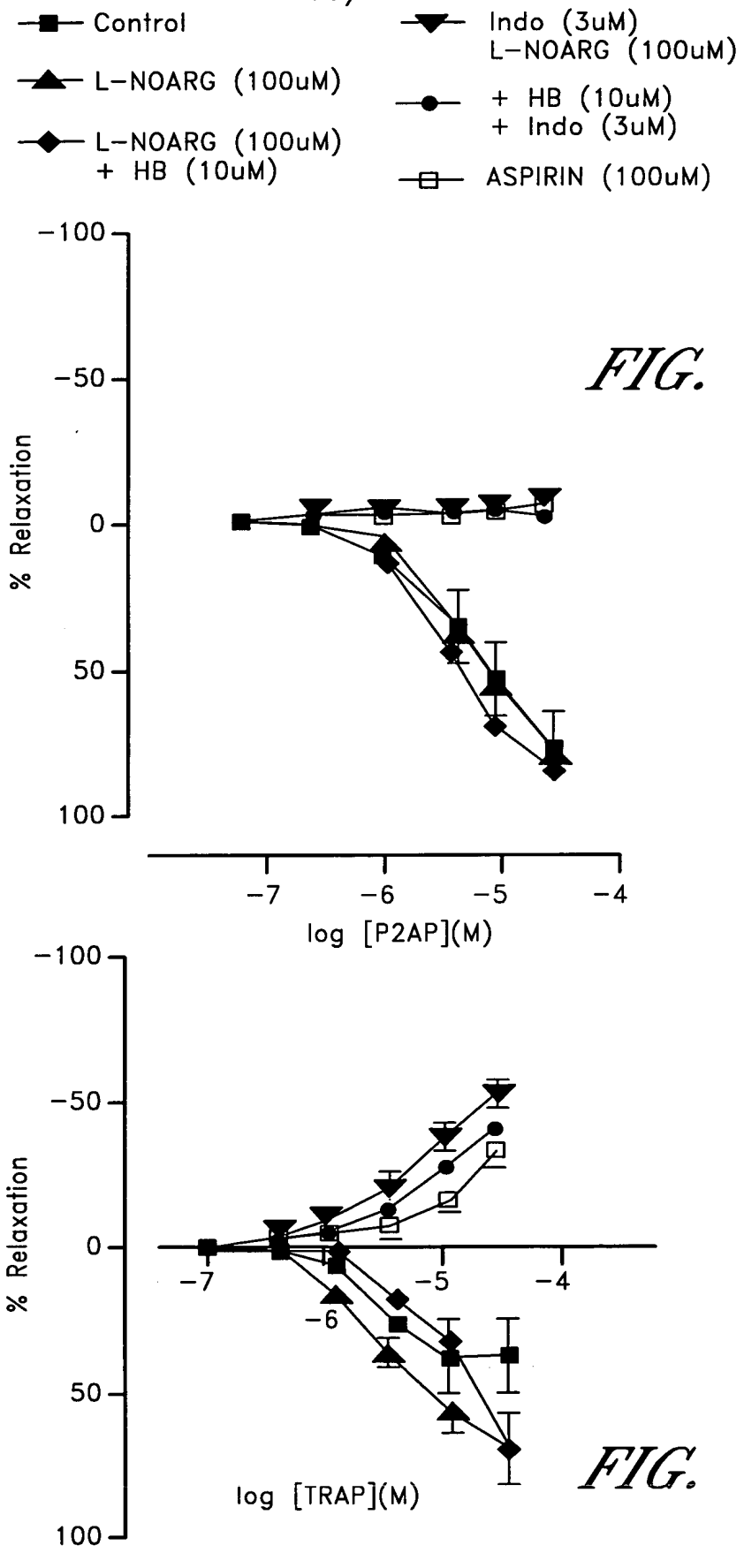
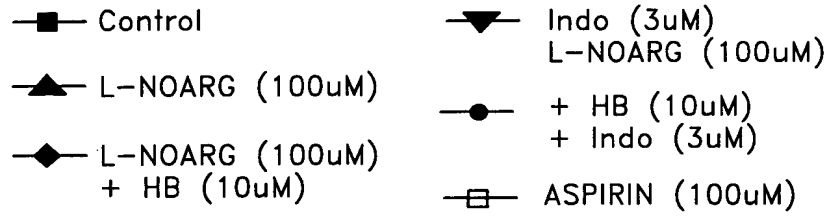

Control
L-NOARG (100uM)
L-NOARG (100uM)
+ HB (10uM)
Indo (3uM)
L-NOARG (100uM)
+ HB (10uM)
+ Indo (3uM)
ASPIRIN (100uM)
-100
-50
0
50
100
% Relaxation
-7
-6
-5
-4
log [P2AP](M)
log [TRAP](M)

FIG. 8A

FIG. 8B


Control
L-NOARG (100uM)
L-NOARG (100uM)
+ HB (10uM)
Indo (3uM)
L-NOARG (100uM)
+ HB (10uM)
+ Indo (3uM)
ASPIRIN (100uM)

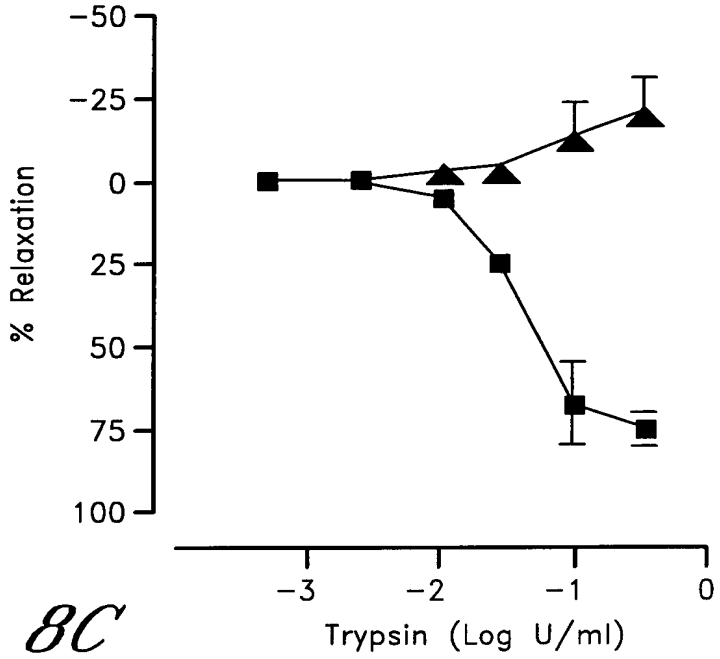

-50
-25
0
25
50
75
100
% Relaxation
-3
-2
-1
0
Trypsin (Log U/ml)

FIG. 8C

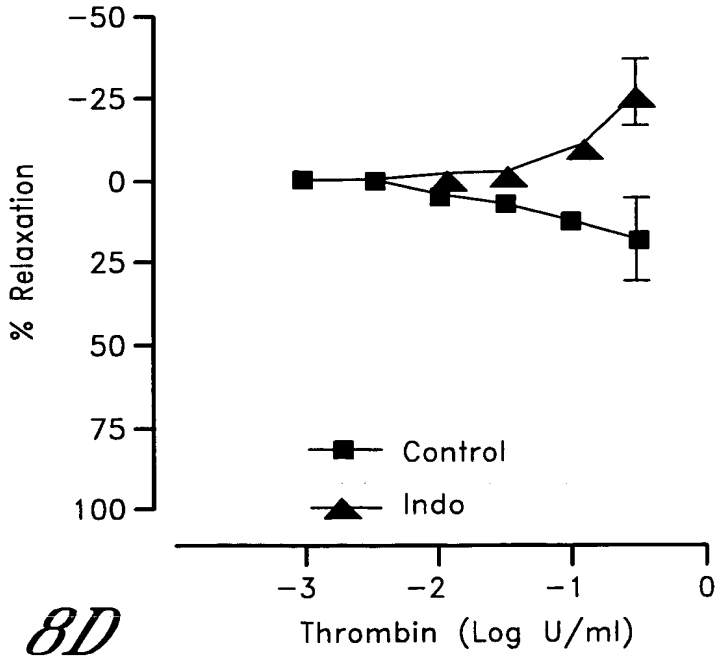
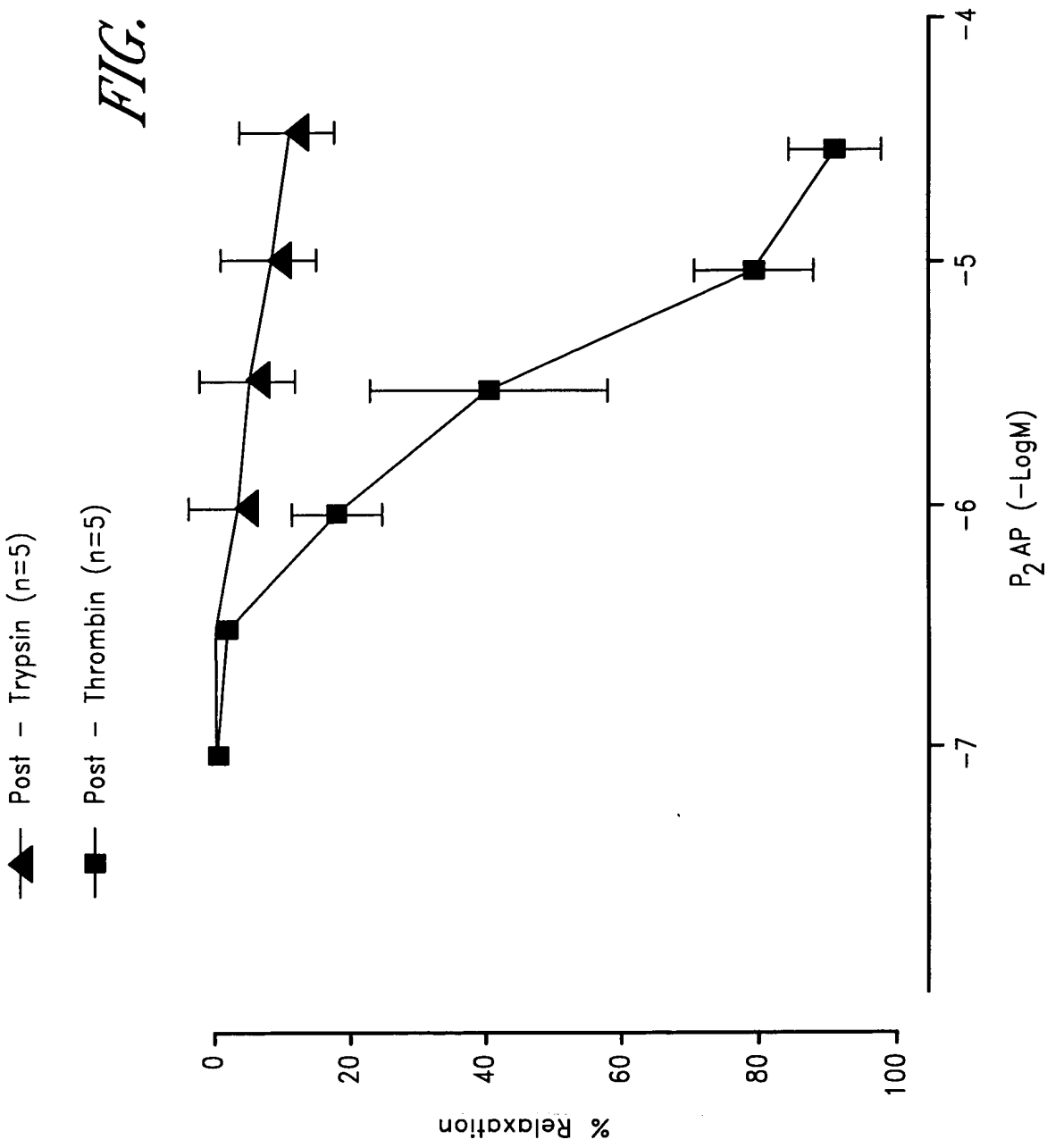

-50
-25
0
25
50
75
100
% Relaxation
Control
Indo
-3
-2
-1
0
Thrombin (Log U/ml)

FIG. 8D

FIG. 9


Post - Trypsin (n=5)
Post - Thrombin (n=5)
% Relaxation
0
20
40
60
80
100
-4
-5
-6
-7
P_2AP (-LogM)

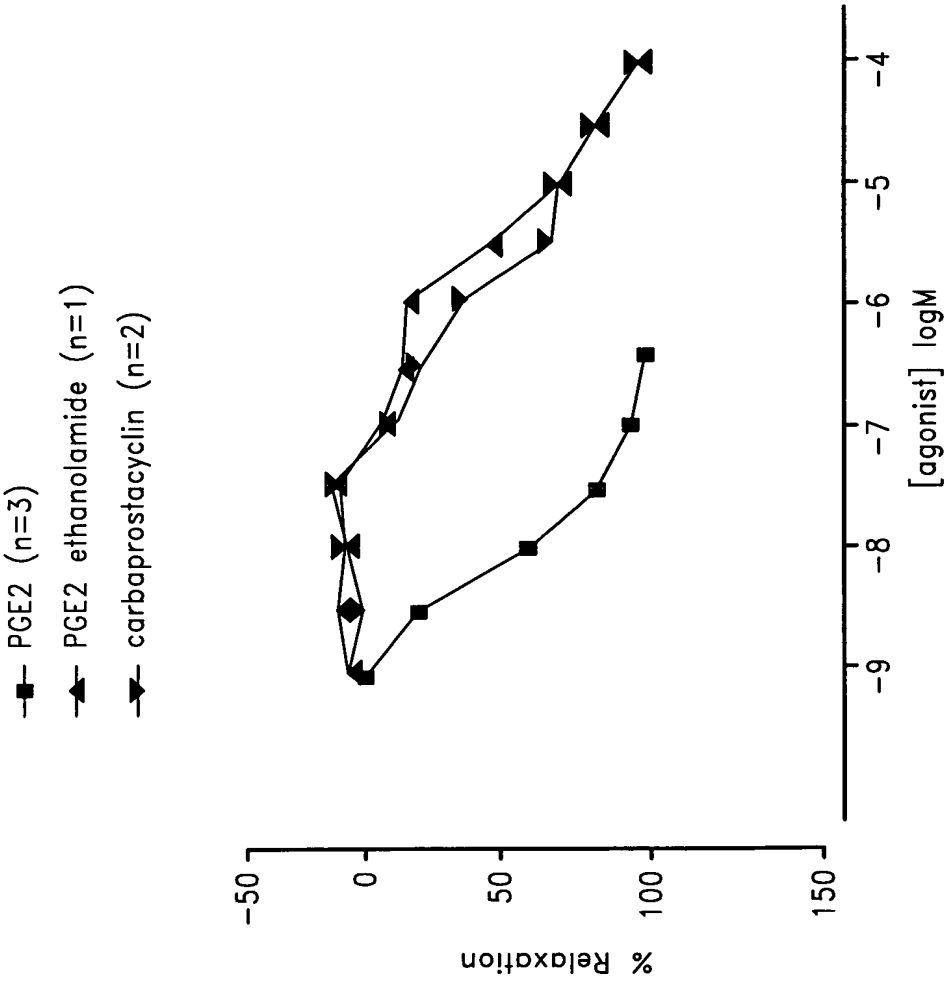

PGE2 (n=3)
PGE2 ethanolamide (n=1)
carbaprostacyclin (n=2)
% Relaxation
-50
0
50
100
150
-9
-8
-7
-6
-5
-4
[agonist] logM

FIG. 10

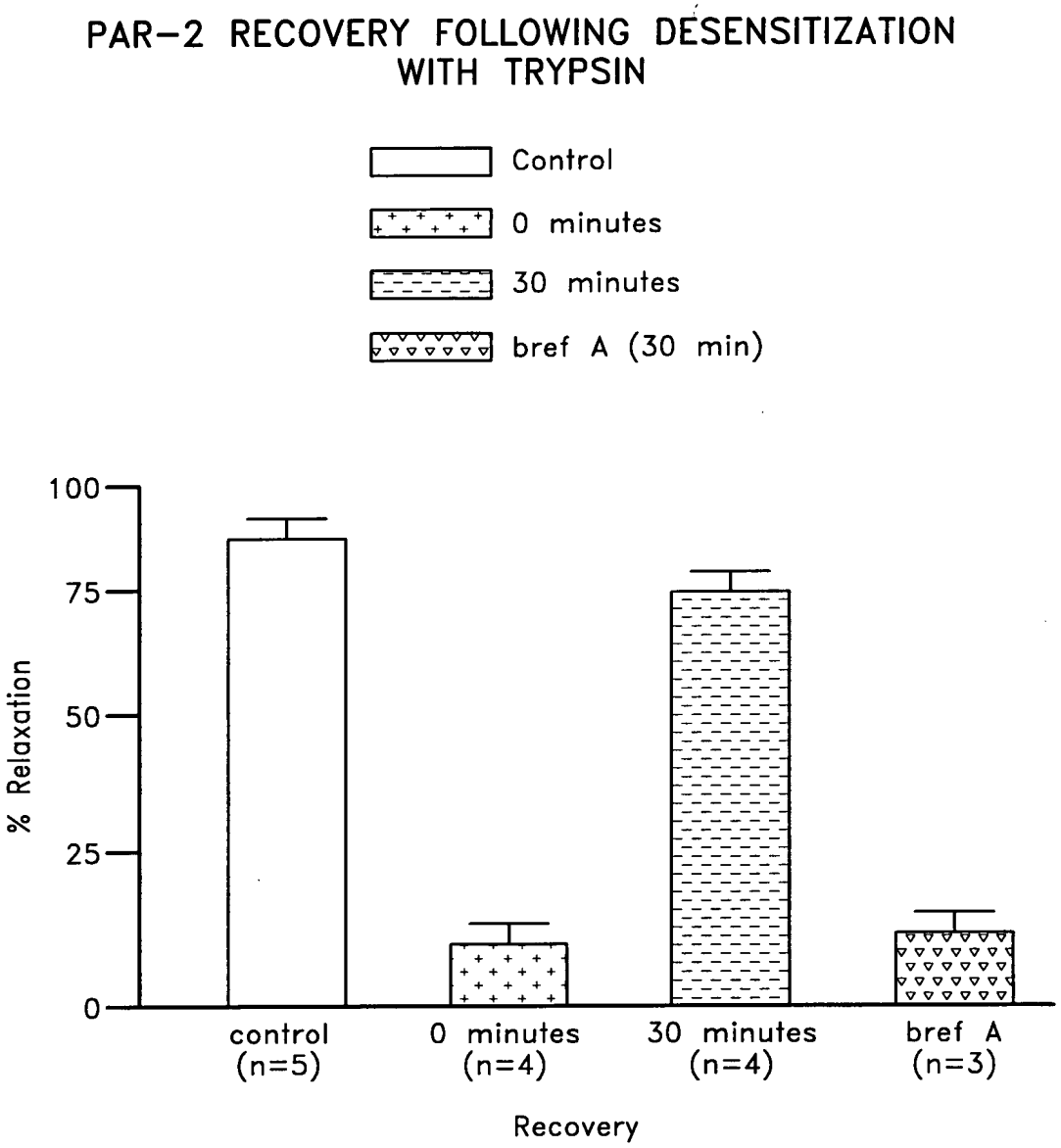

PAR-2 RECOVERY FOLLOWING DESENSITIZATION WITH TRYPSIN
Control
0 minutes
30 minutes
bref A (30 min)
100
75
50
25
0
% Relaxation
control (n=5)
0 minutes (n=4)
30 minutes (n=4)
bref A (n=3)
Recovery

FIG. 11A

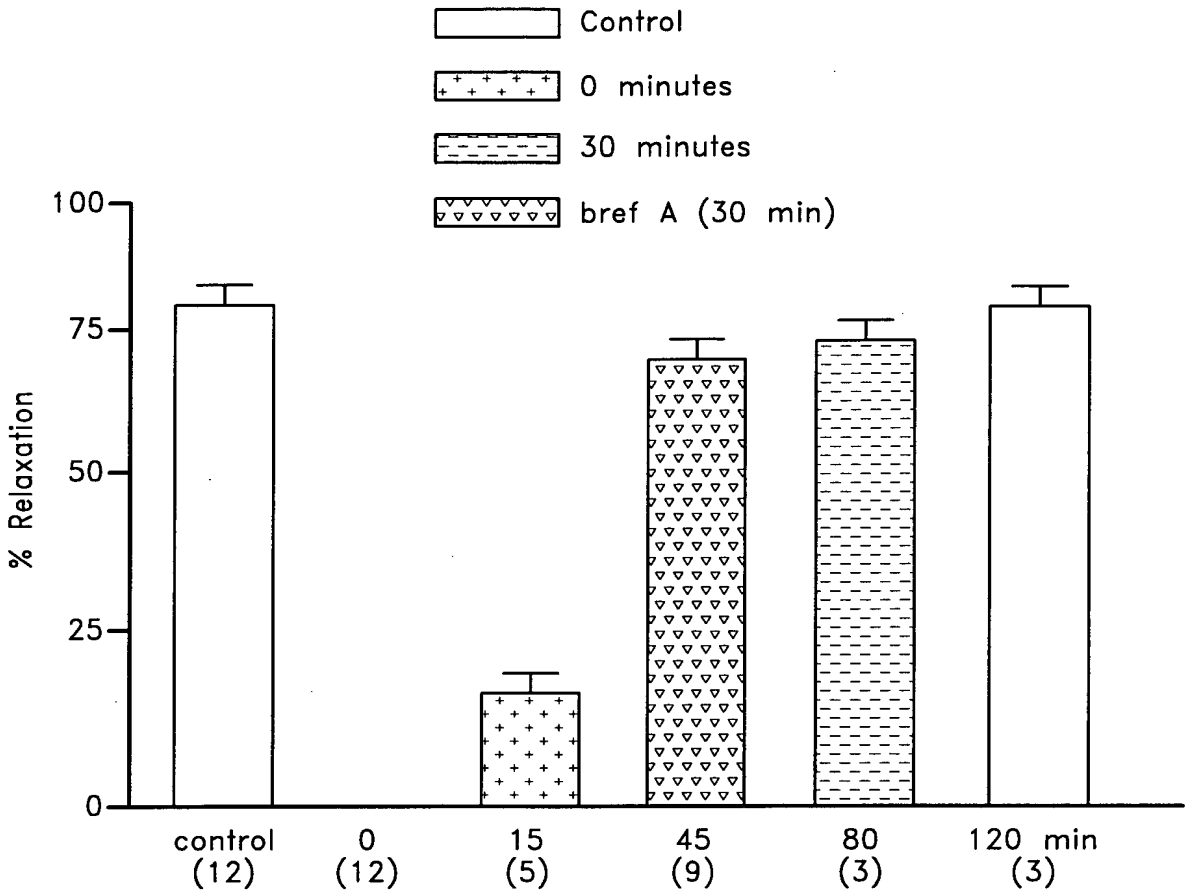


FIG. 11B

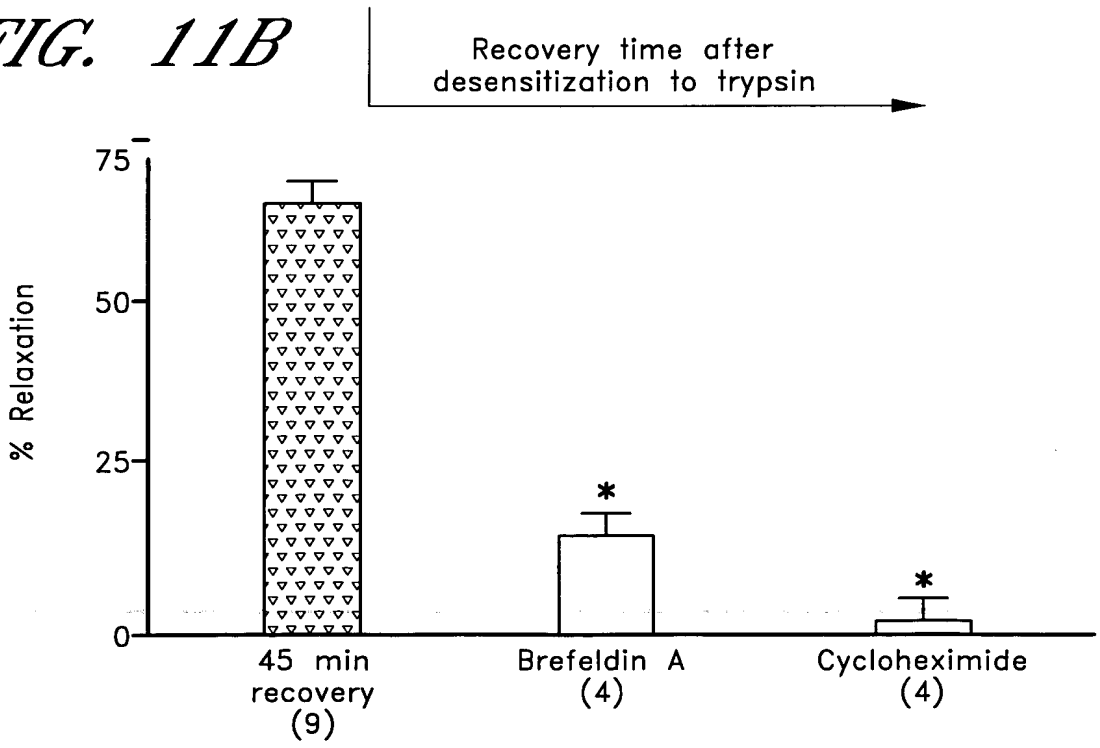


FIG. 11C

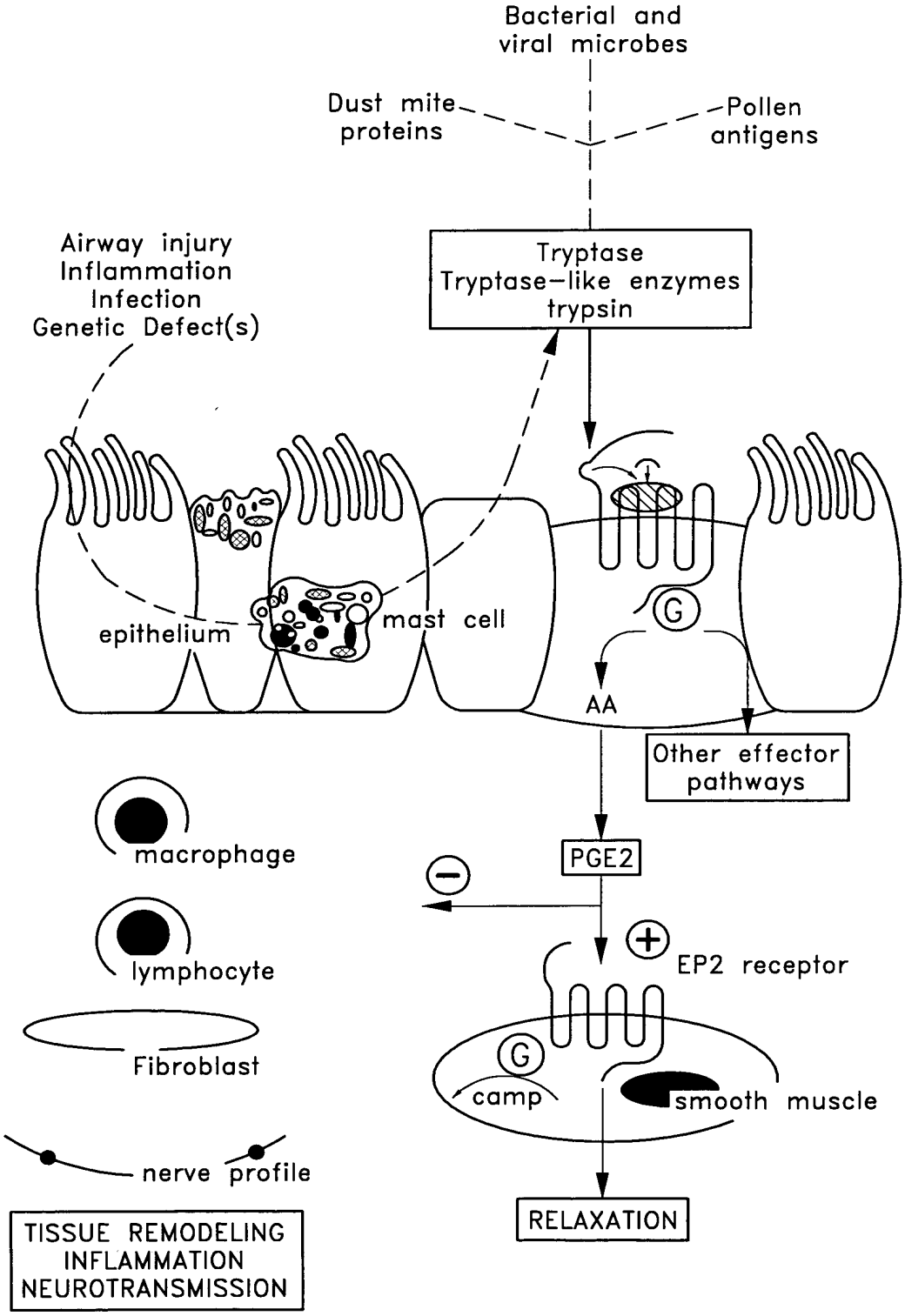

Bacterial and viral microbes
Dust mite proteins
Pollen antigens
Airway injury
Inflammation
Infection
Genetic Defect(s)
Tryptase
Tryptase–like enzymes
trypsin
epithelium
mast cell
G
AA
Other effector pathways
macrophage
lymphocyte
Fibroblast
nerve profile
TISSUE REMODELING
INFLAMMATION
NEUROTRANSMISSION
PGE2
EP2 receptor
G
camp
smooth muscle
RELAXATION

FIG. 12

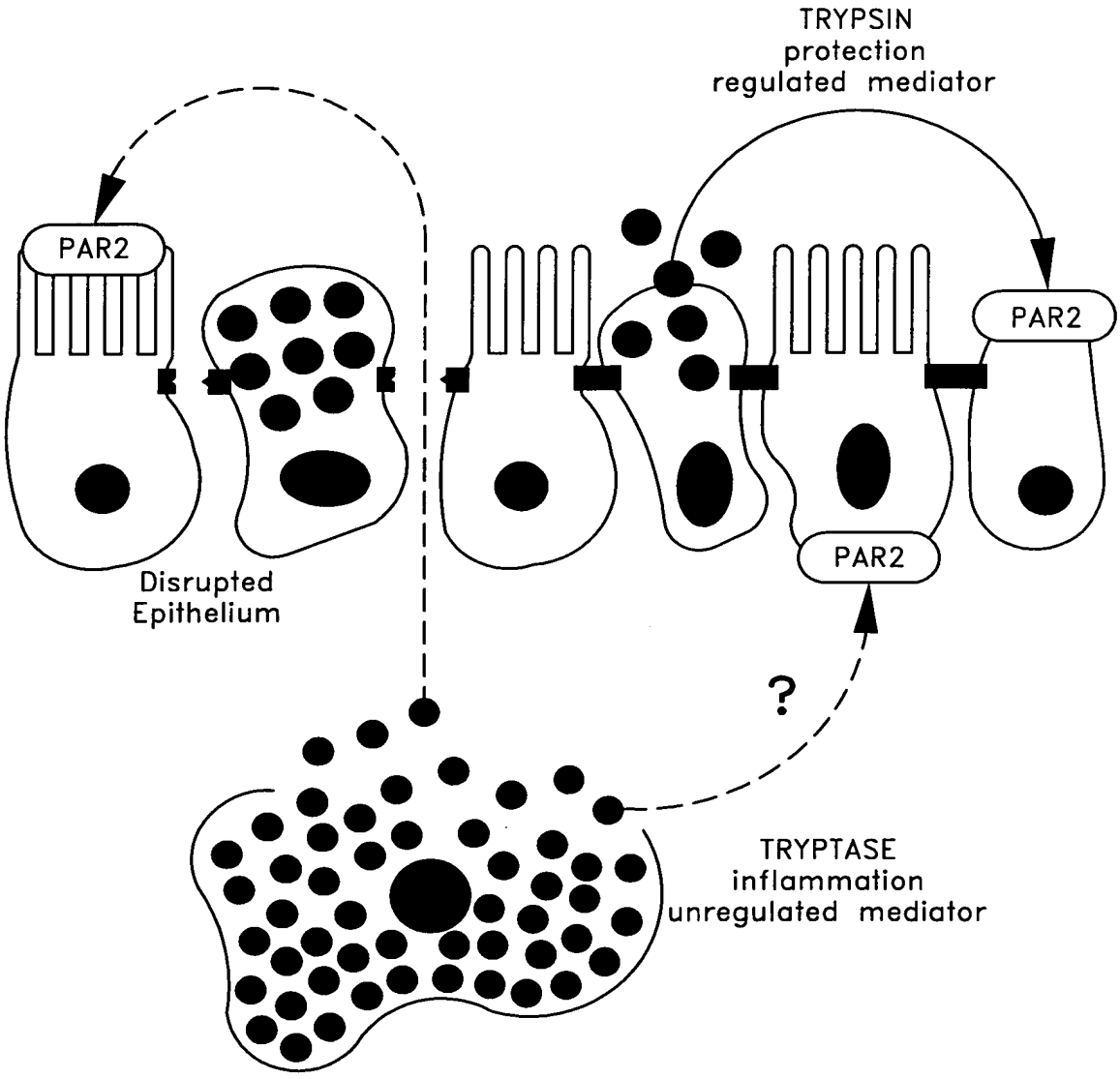

TRYPSIN
protection
regulated mediator
PAR2
PAR2
PAR2
Disrupted
Epithelium
?
TRYPTASE
inflammation
unregulated mediator

FIG. 13

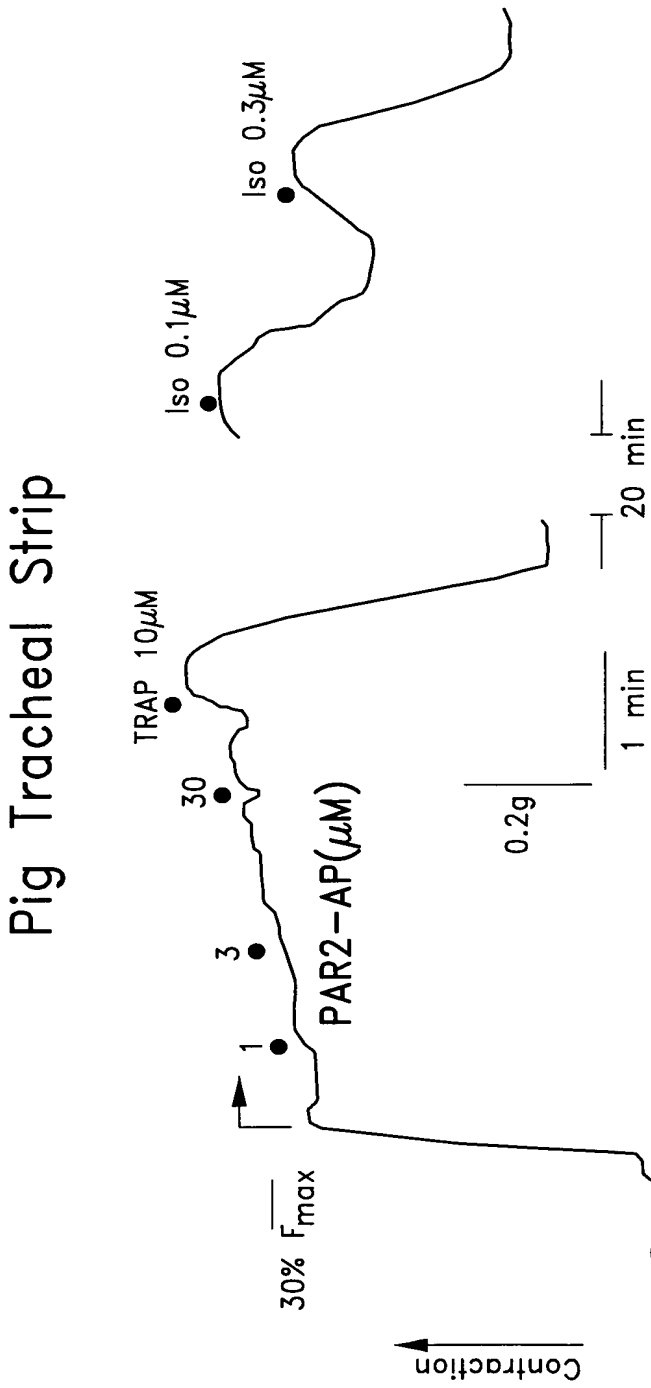

Pig Tracheal Strip
Iso 0.1μM
Iso 0.3μM
TRAP 10μM
30
3
1
PAR2-AP(μM)
0.2g
1 min
20 min
30% $\overline{F_{max}}$
Carbachol 40nM
Contraction

FIG. 14

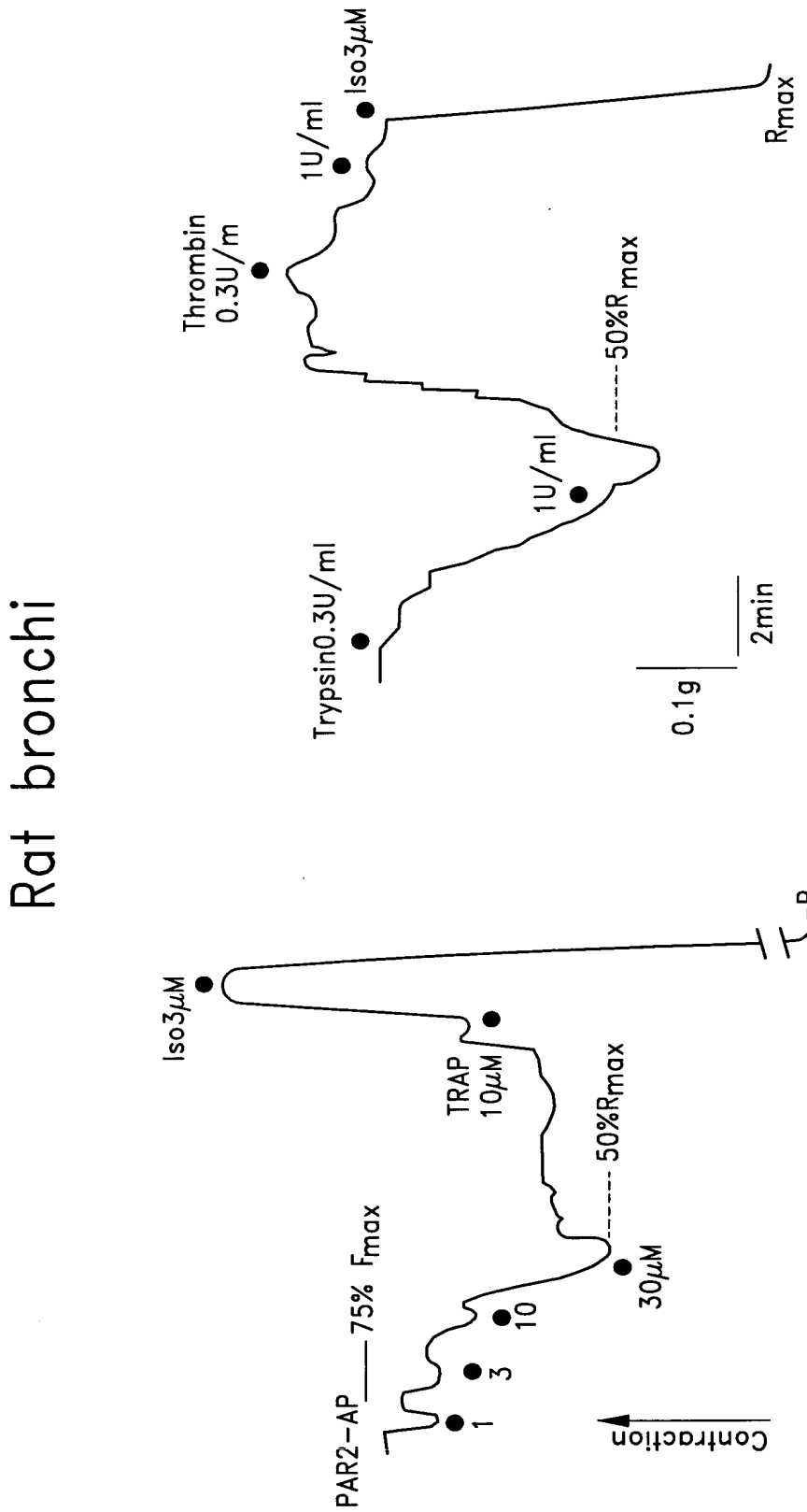


FIG. 15A

FIG. 15B

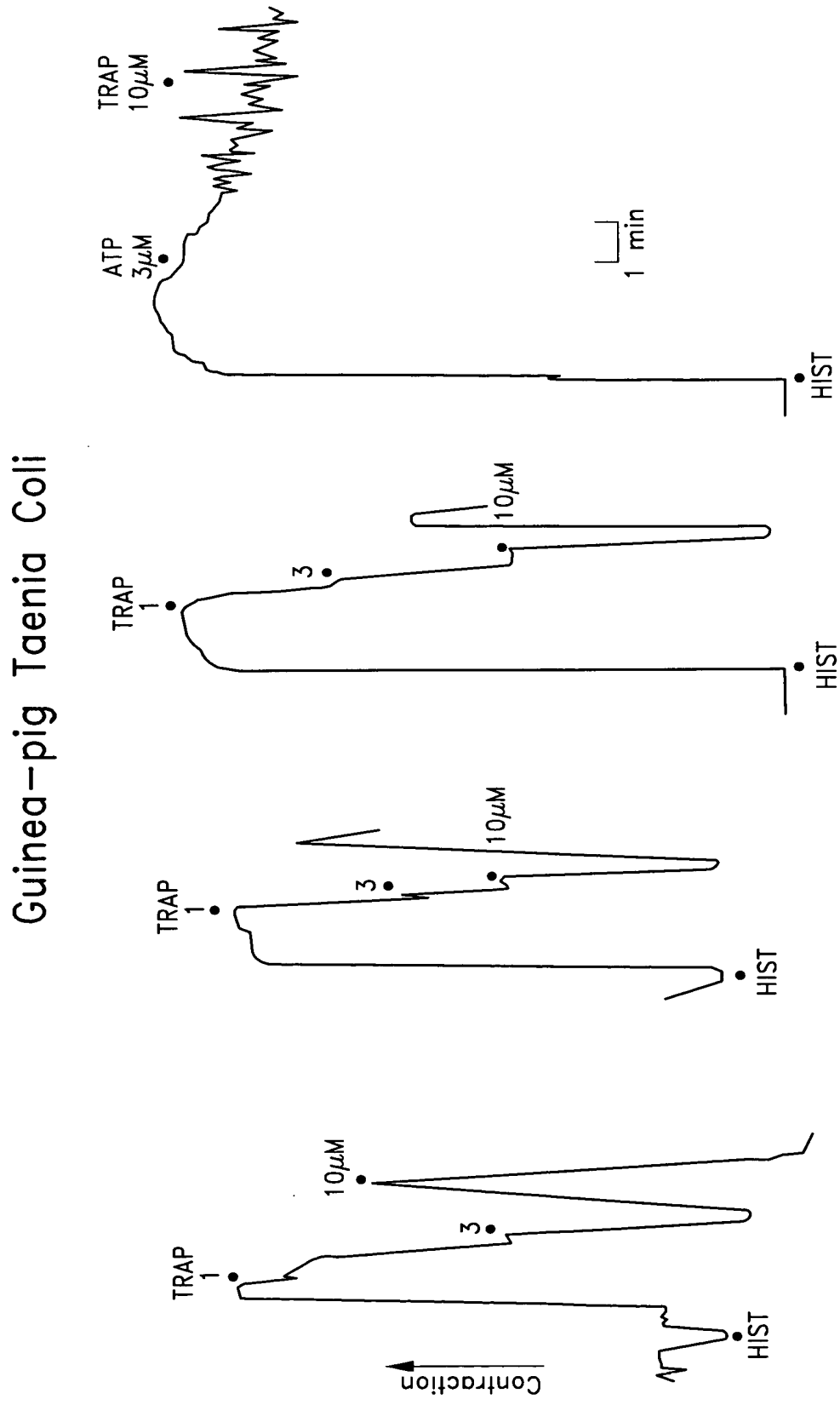


FIG. 16A FIG. 16B FIG. 16C FIG. 16D

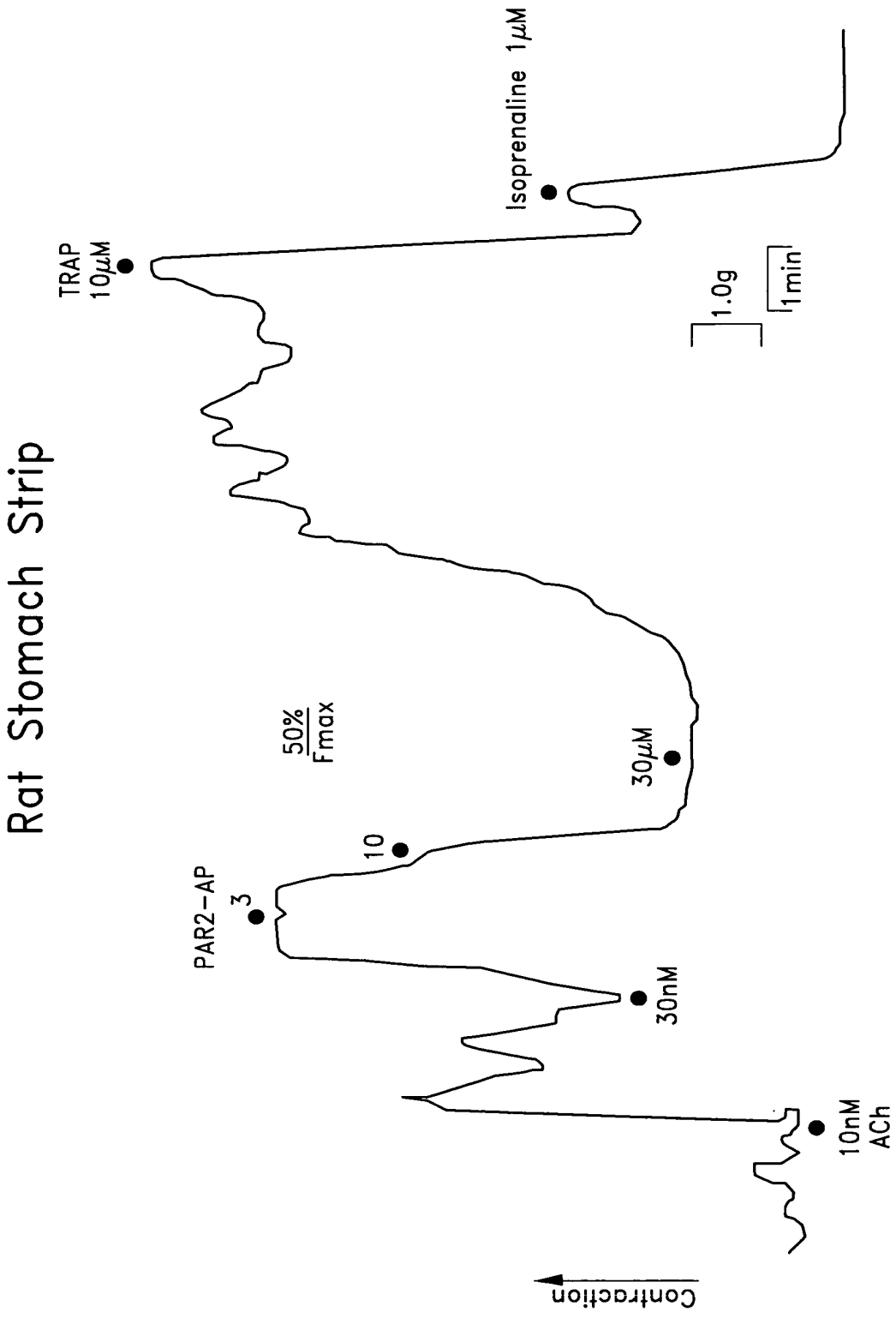

Rat Stomach Strip
TRAP
10μM
Isoprenaline 1μM
1.0g
1min
50%
Fmax
30μM
10
PAR2-AP
3
30nM
10nM
ACh
Contraction

FIG. 17

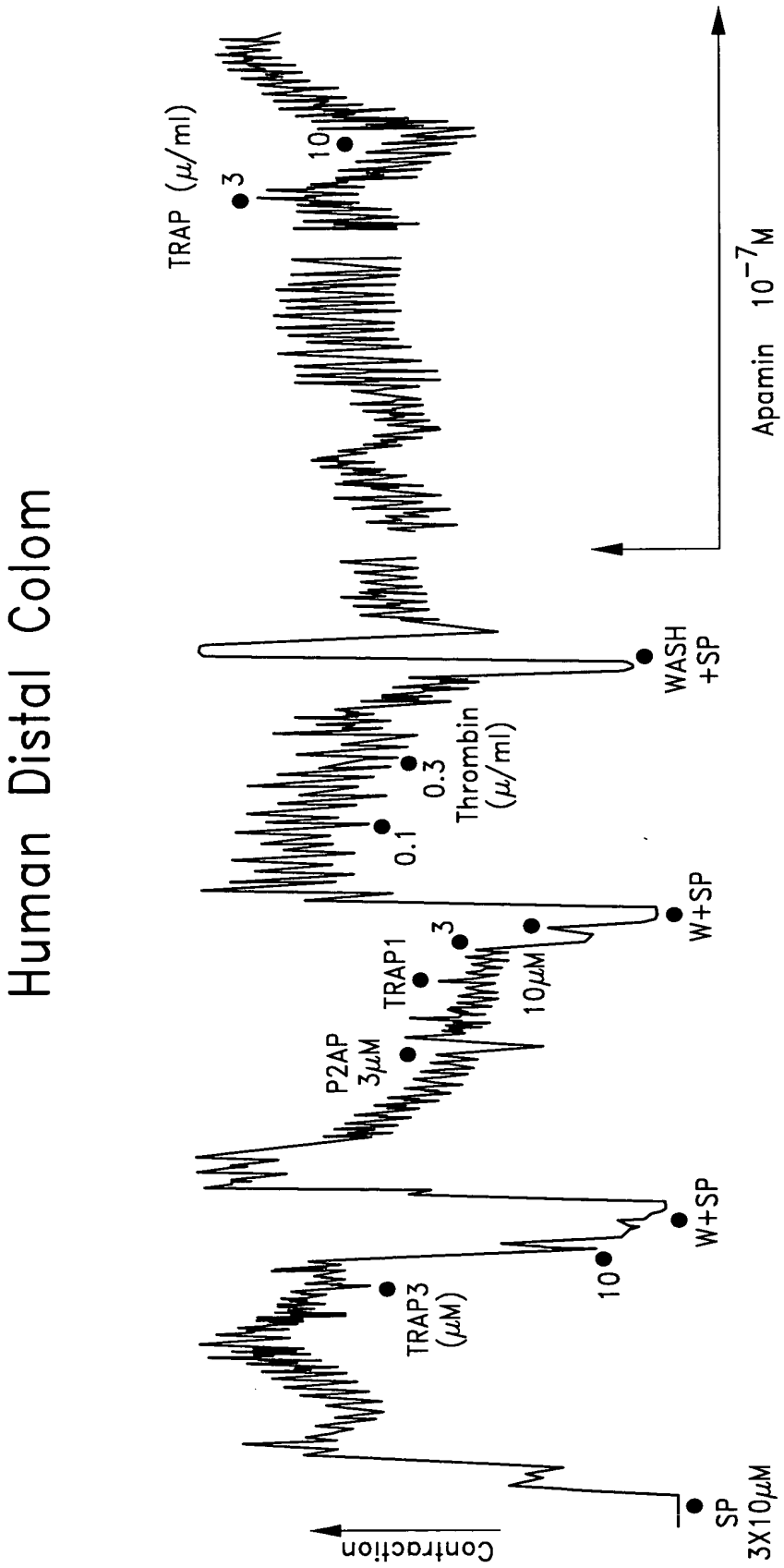

Human Distal Colom
Contraction
SP
3X10μM
TRAP3
(μM)
10
W+SP
P2AP
3μM
TRAP1
3
10μM
W+SP
0.1
0.3
Thrombin
(μ/ml)
WASH
+SP
TRAP (μ/ml)
3
10
Apamin 10⁻⁷M

FIG. 18

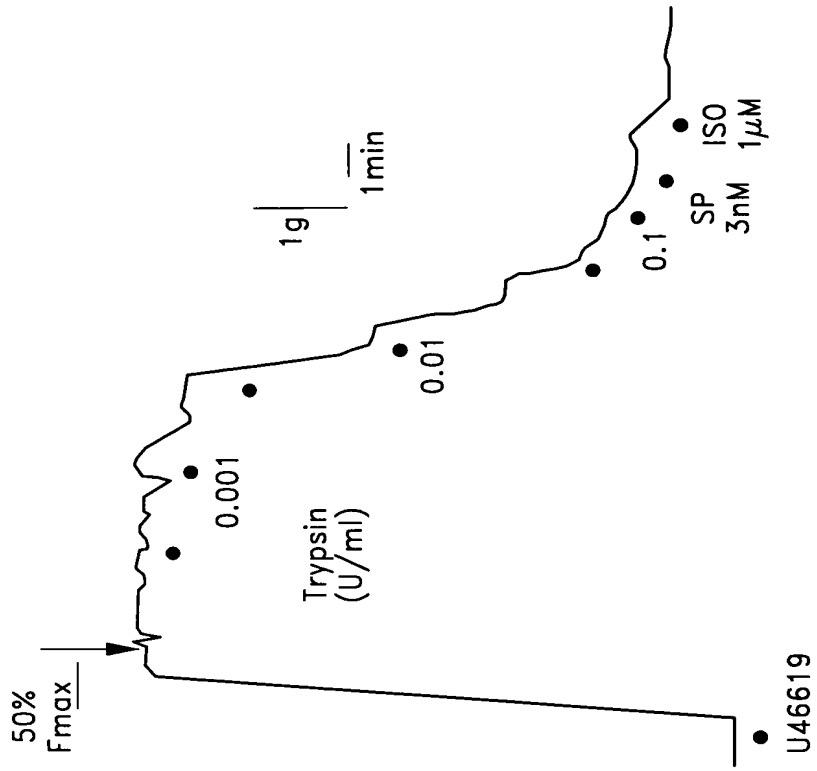


FIG. 19B

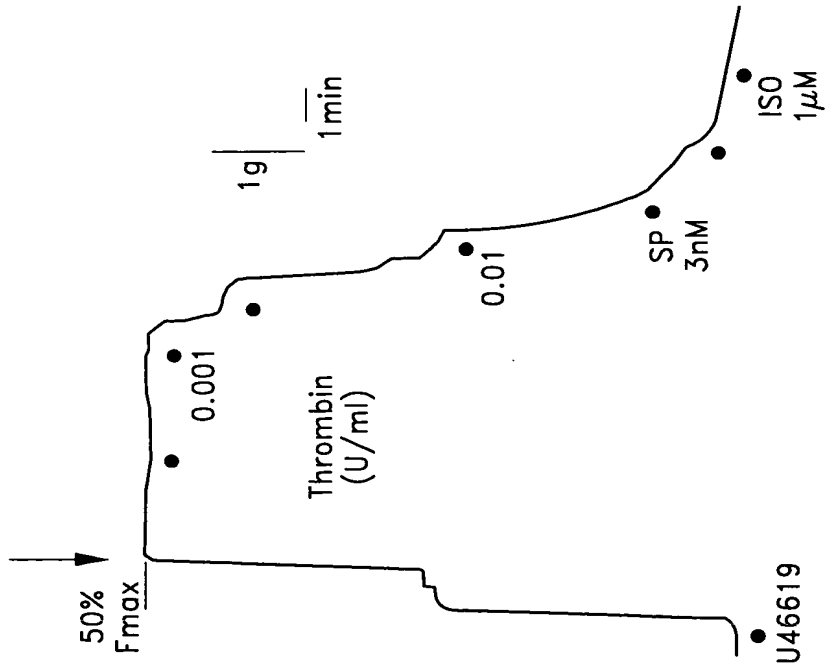


FIG. 19A

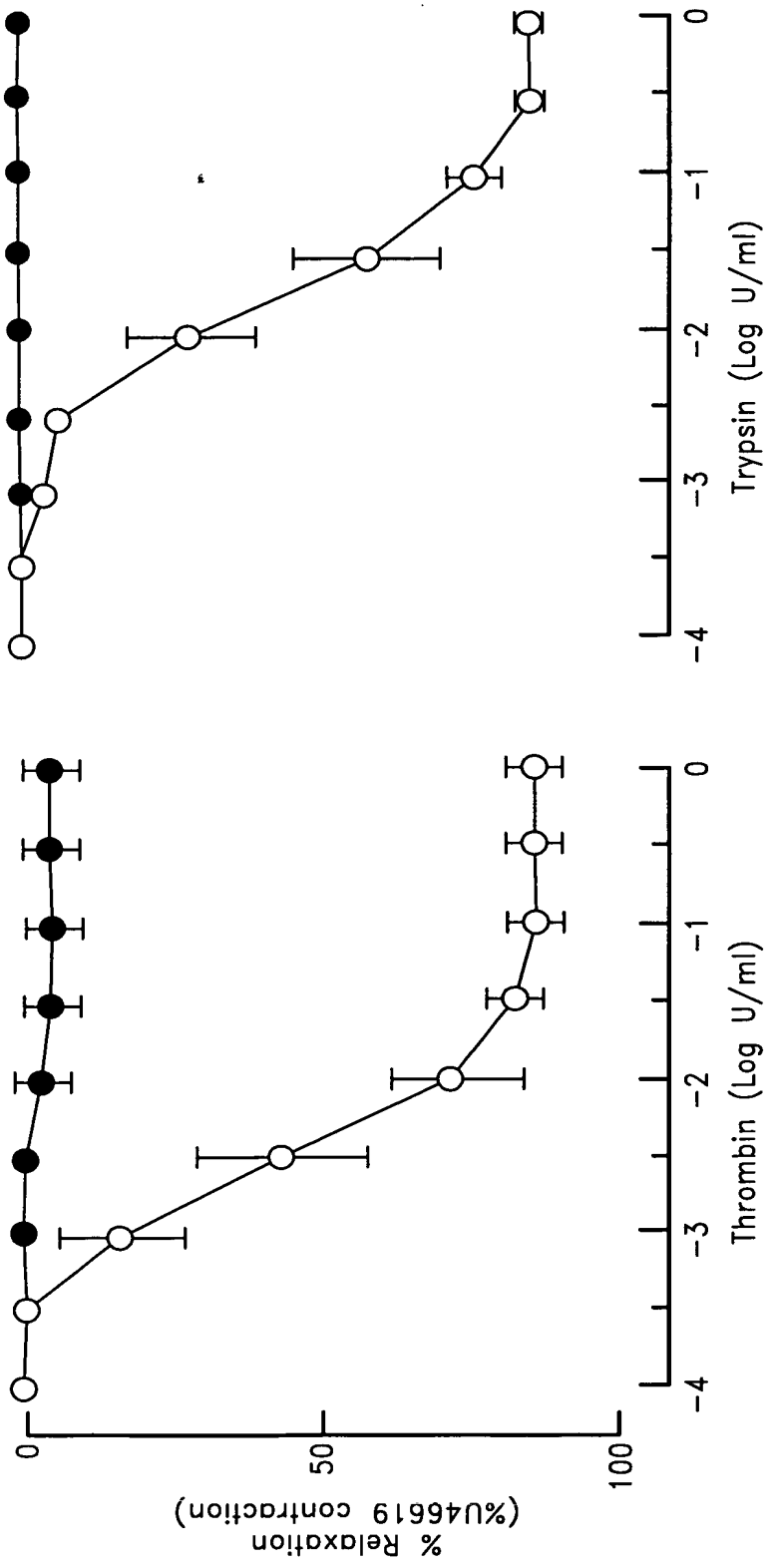


FIG. 19C

FIG. 19D

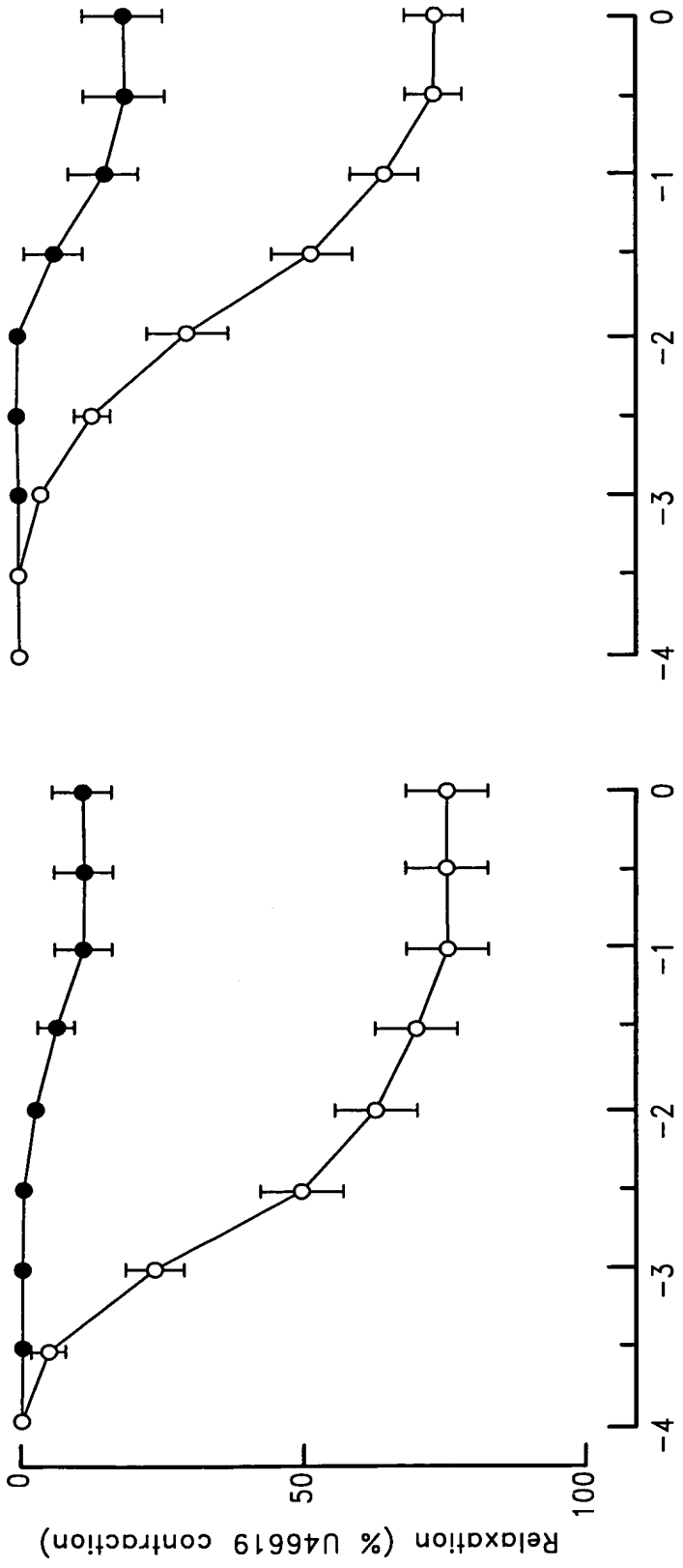


FIG. 20A

FIG. 20B

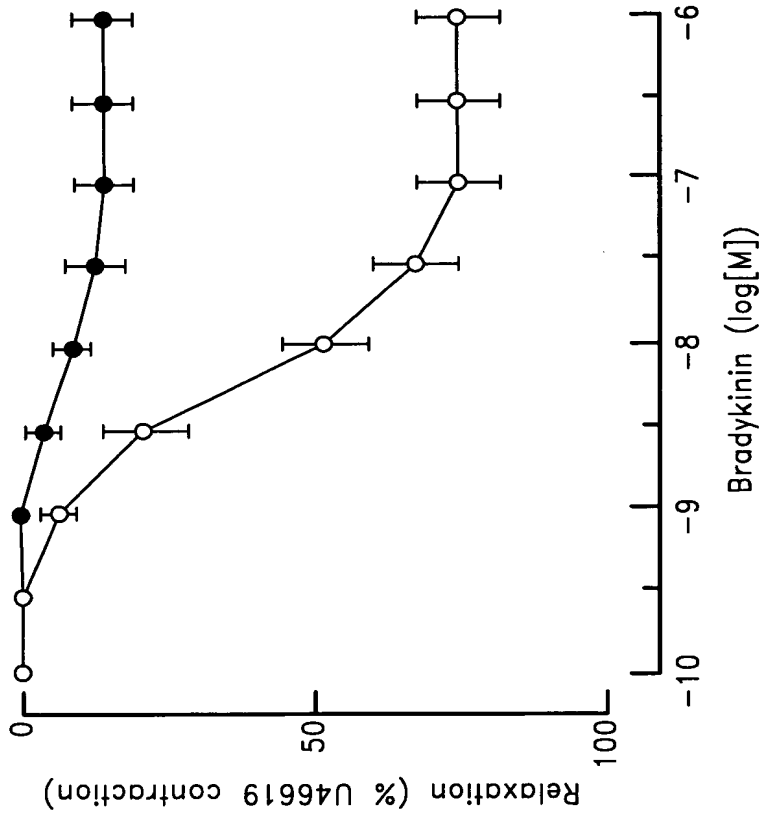

Relaxation (% U46619 contraction)
0
50
100
-10
-9
-8
-7
-6
Bradykinin (log[M])

FIG. 20C

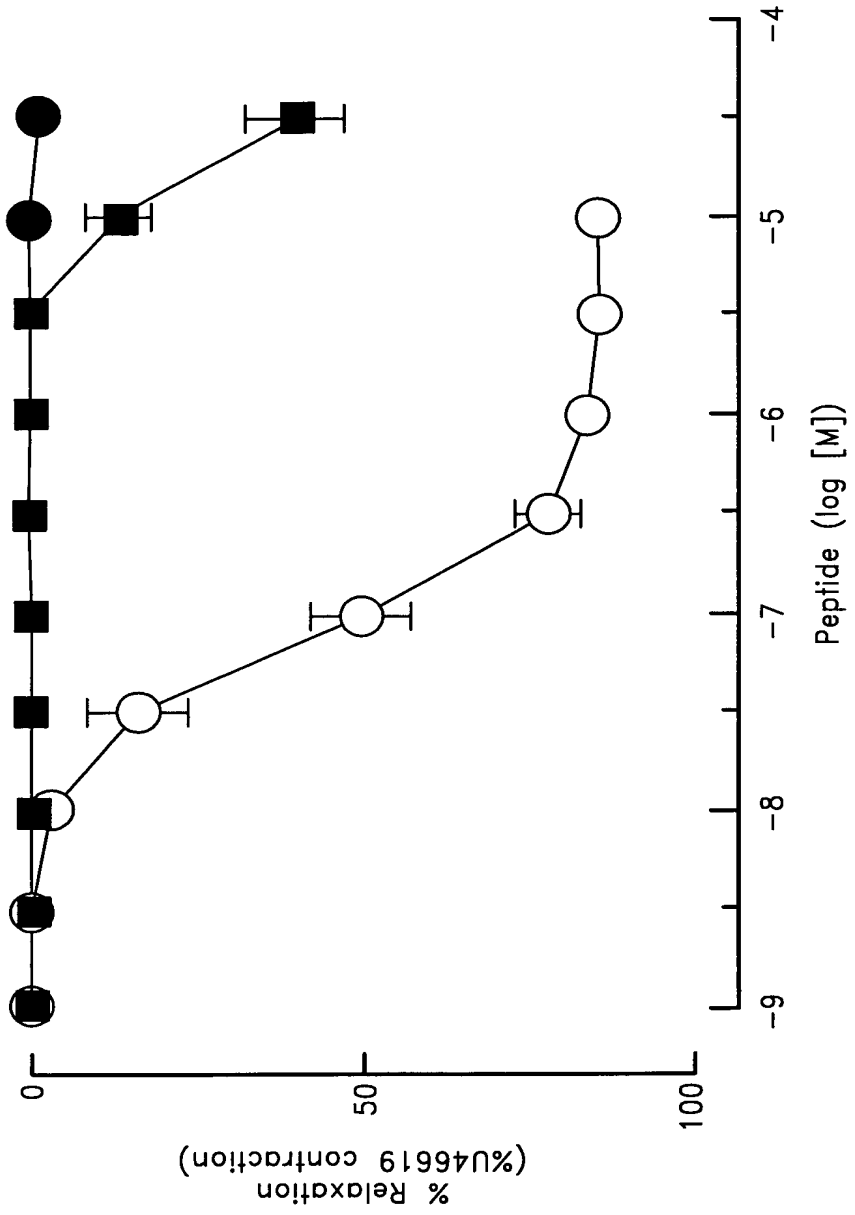

% Relaxation
(%U46619 contraction)
0
50
100
-9
-8
-7
-6
-5
-4
Peptide (log [M])

FIG. 21

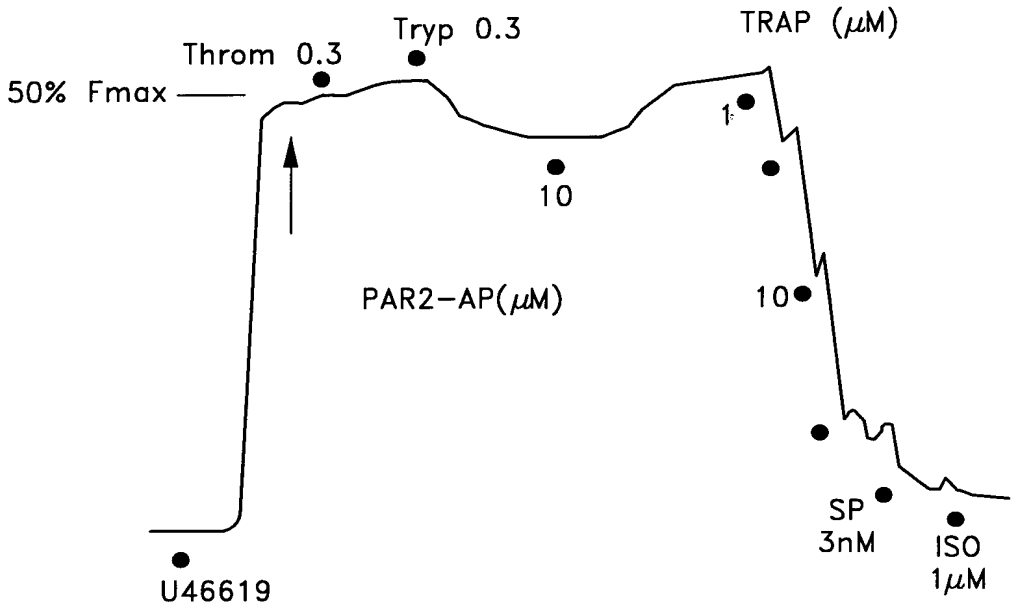


FIG. 22A

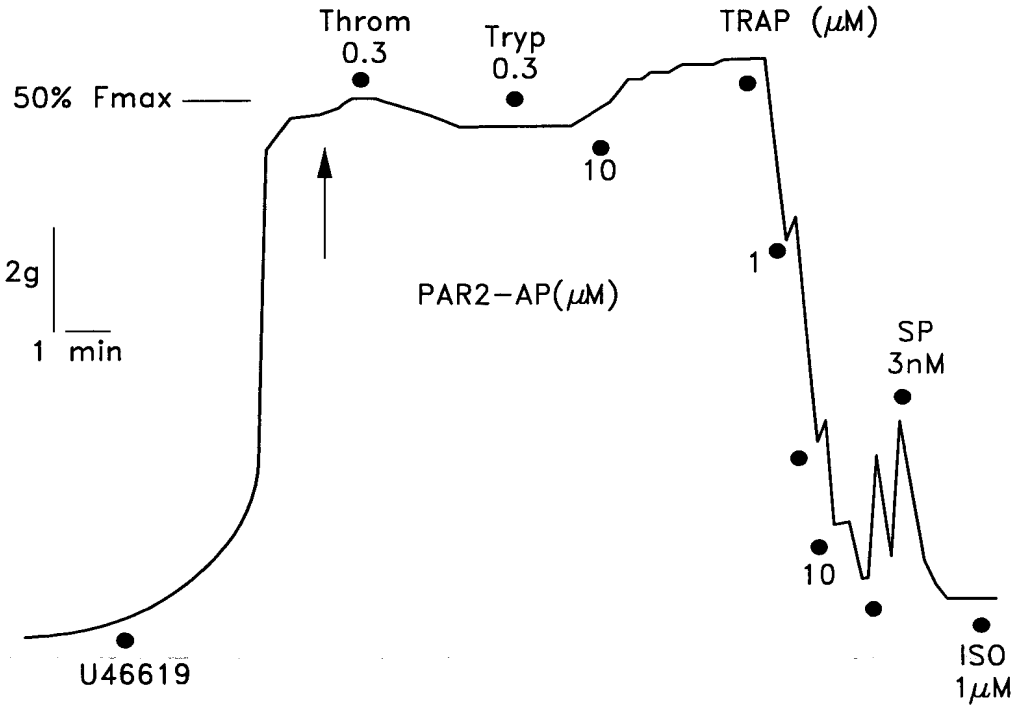


FIG. 22B

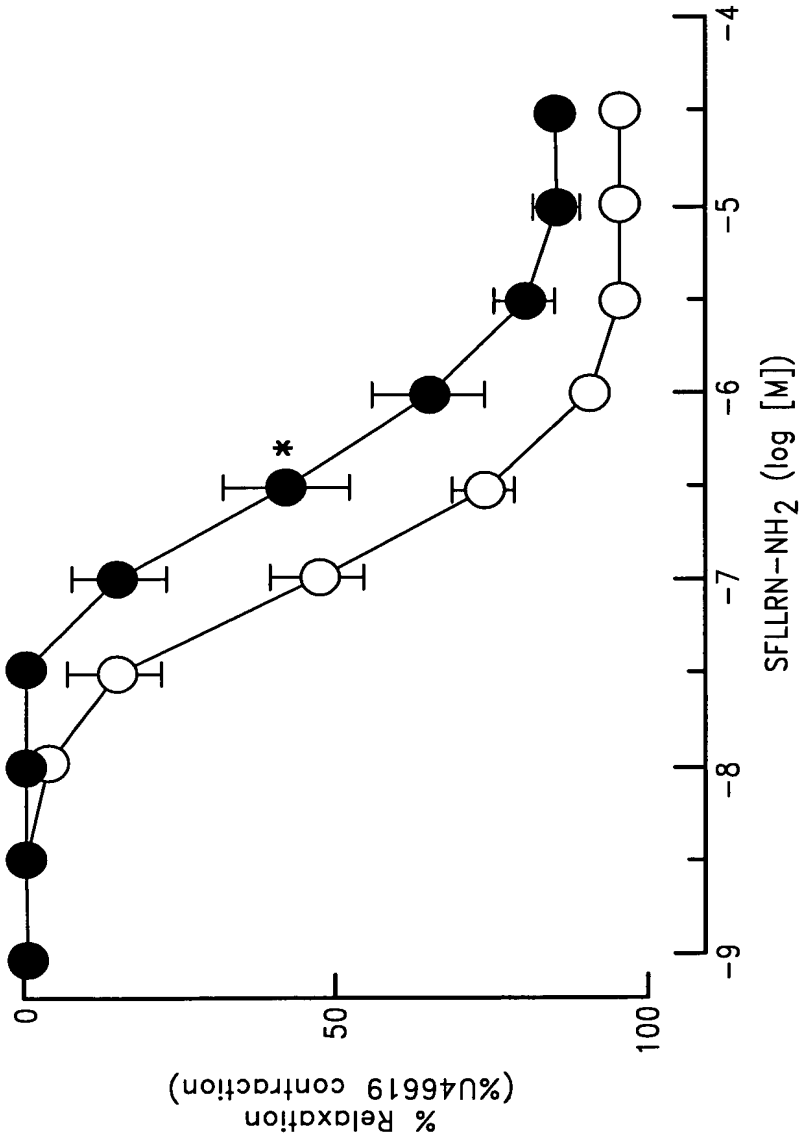

% Relaxation
(%U46619 contraction)
0
50
100
*
-9
-8
-7
-6
-5
-4
SFLLRN-NH2 (log [M])

FIG. 23

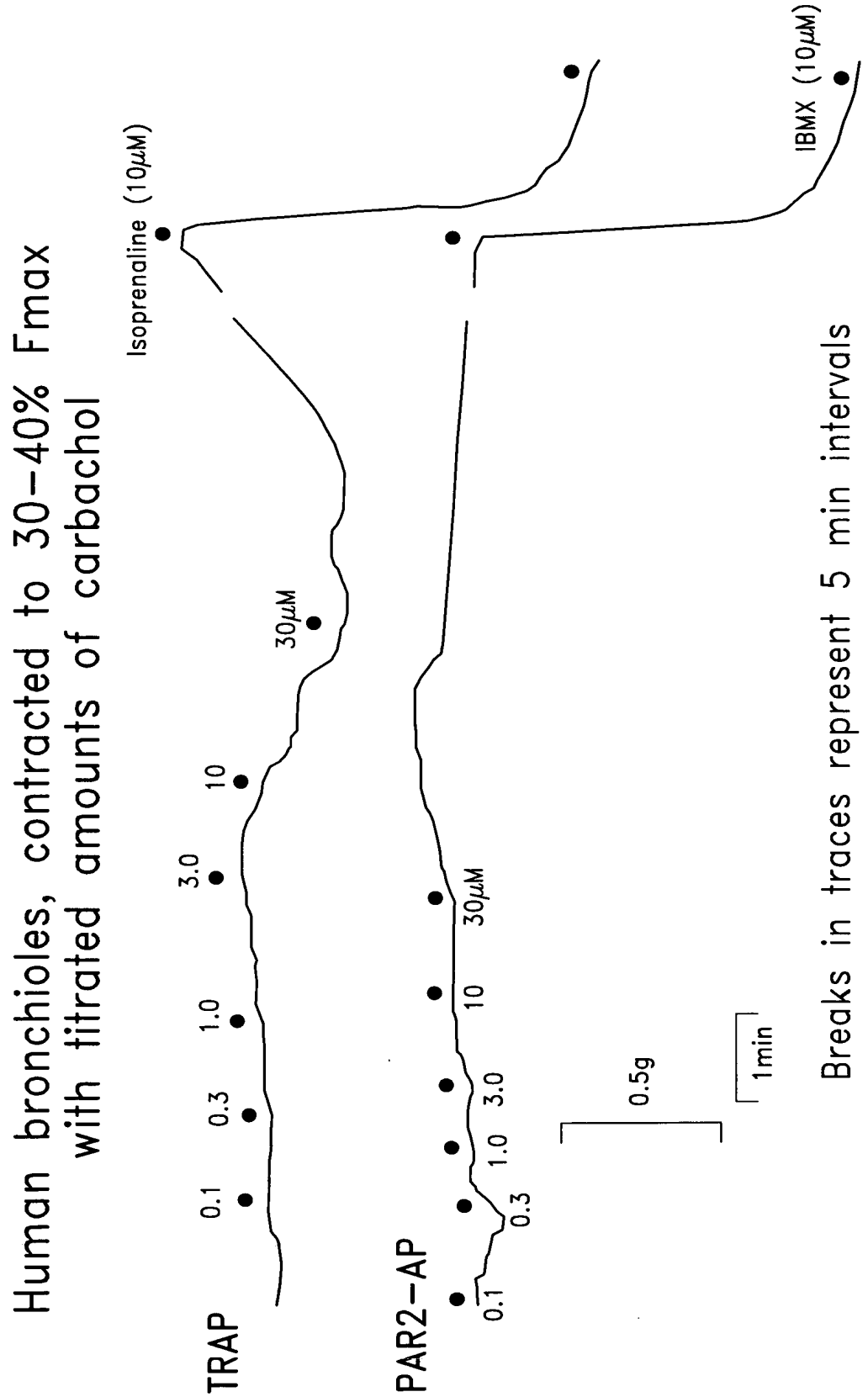

Human bronchioles, contracted to 30–40% Fmax
with titrated amounts of carbachol
Isoprenaline (10μM)
IBMX (10μM)
TRAP
PAR2–AP
0.1
0.3
1.0
3.0
10
30μM
0.5g
1min
Breaks in traces represent 5 min intervals

FIG. 24

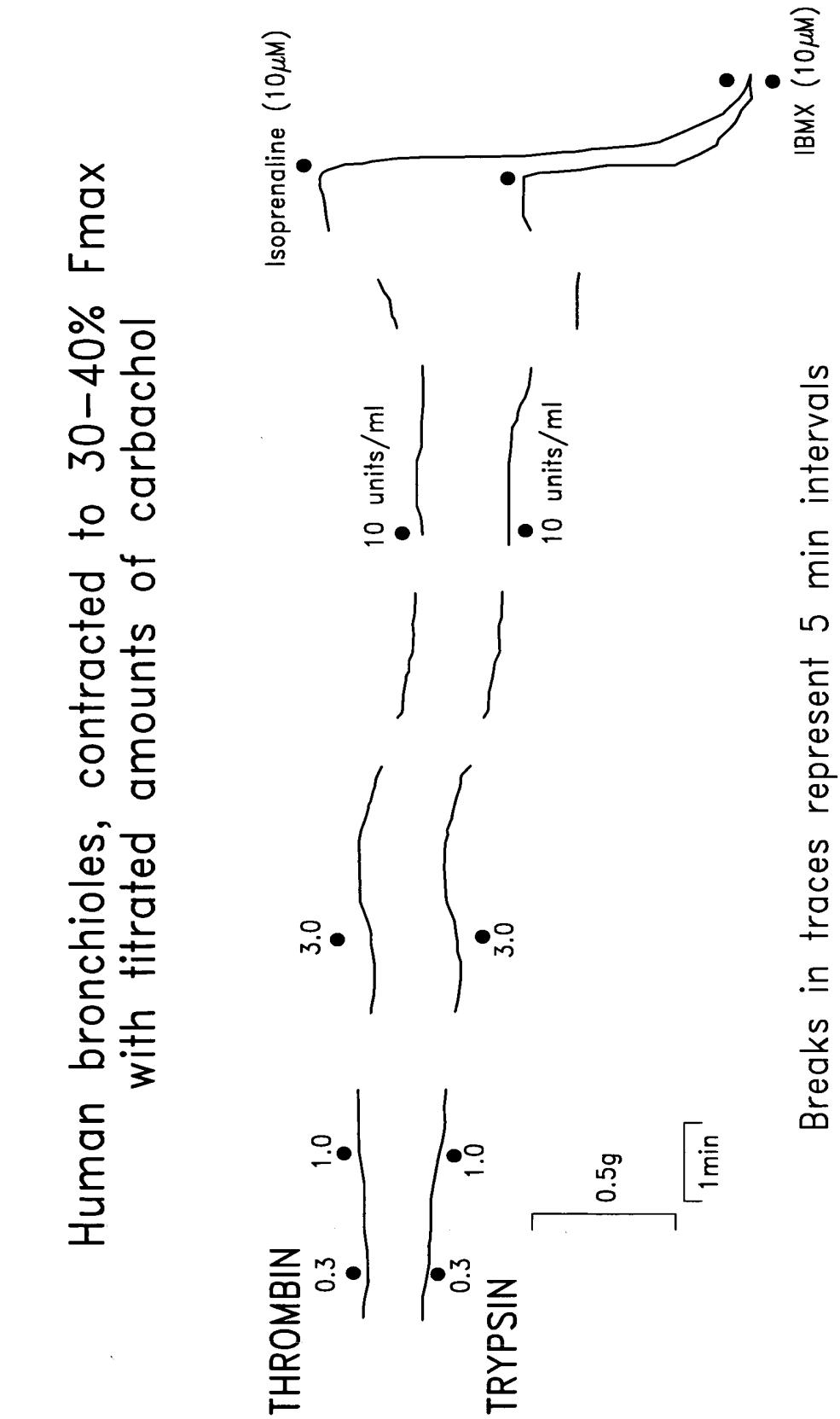

Human bronchioles, contracted to 30–40% Fmax
with titrated amounts of carbachol
THROMBIN
TRYPSIN
0.3
1.0
3.0
10 units/ml
Isoprenaline (10μM)
IBMX (10μM)
0.5g
1min
Breaks in traces represent 5 min intervals

FIG. 25

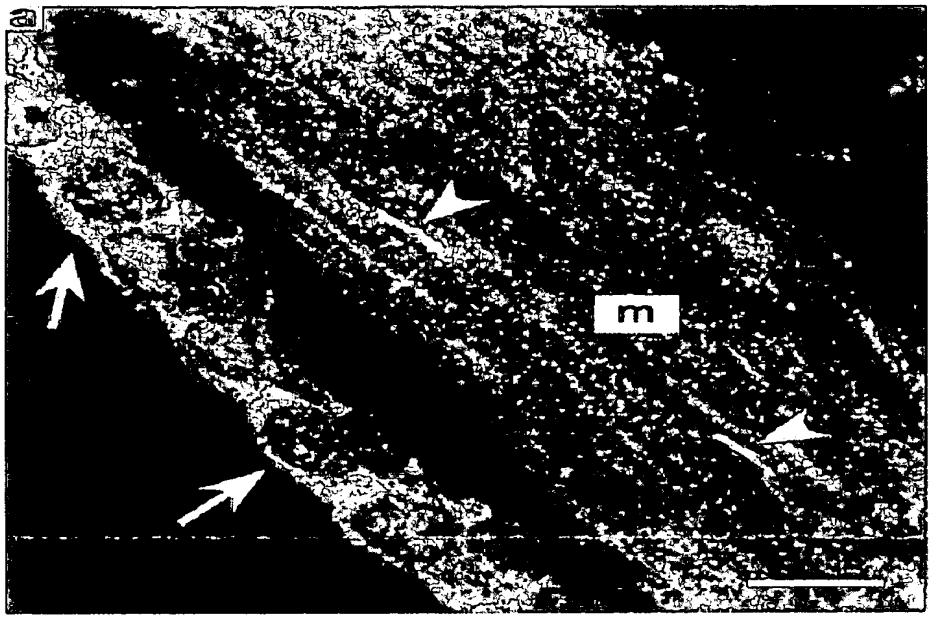


FIG. 26A

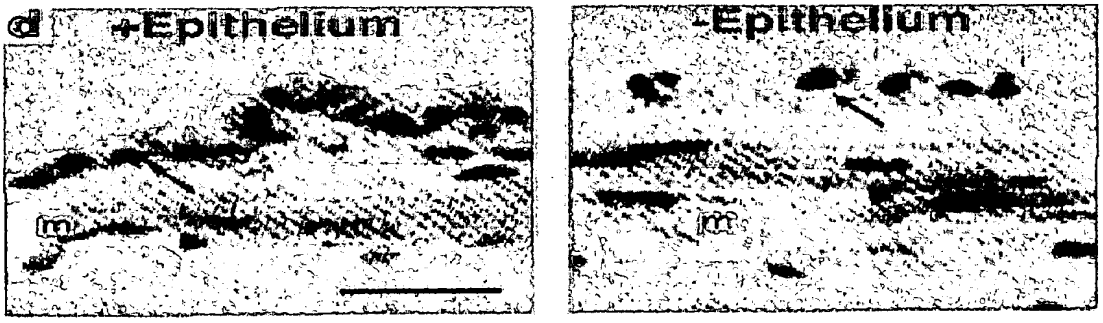


FIG. 26D

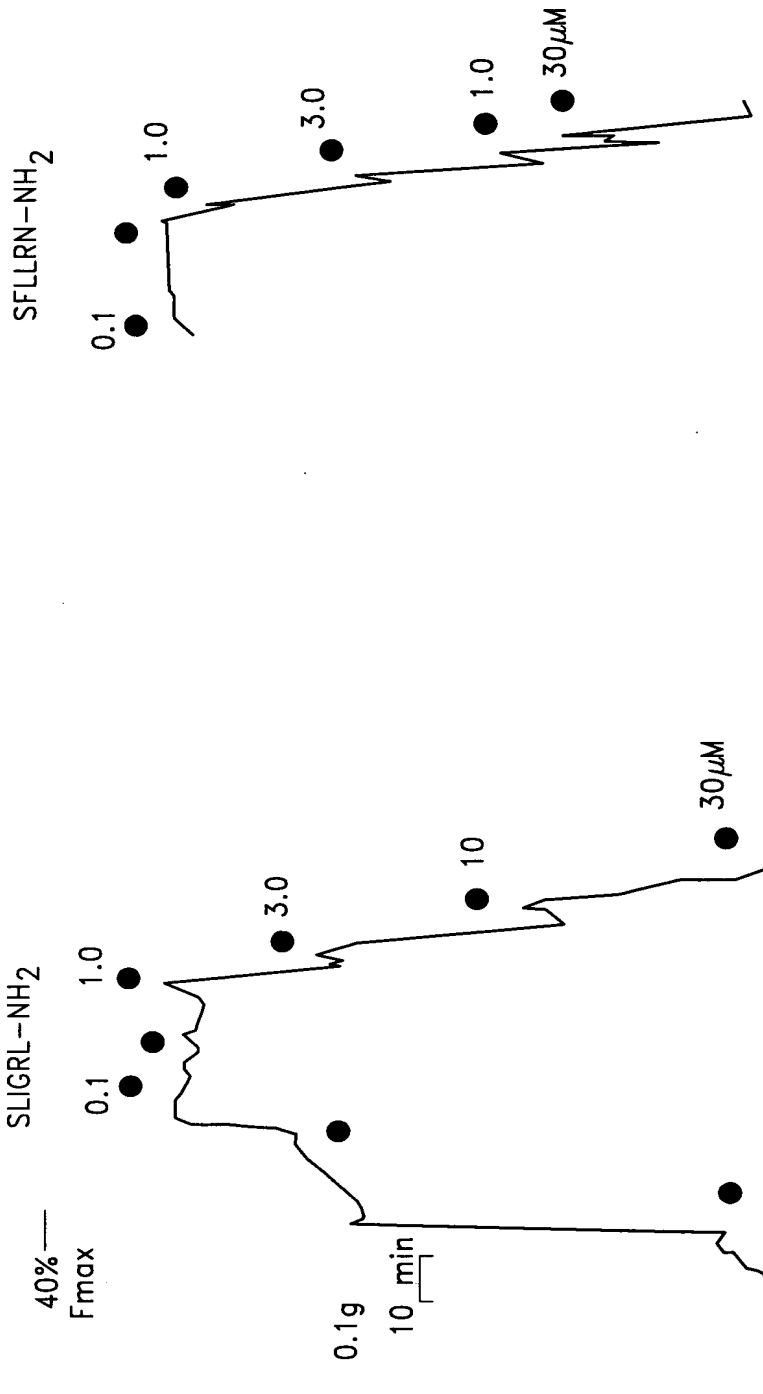

SFLLRN-NH2
0.1
1.0
1.0
3.0
1.0
30μM
SLIGRL-NH2
0.1
1.0
3.0
10
30μM
Carbachol
15min
40%
Fmax
0.1g
10 min

FIG. 26B

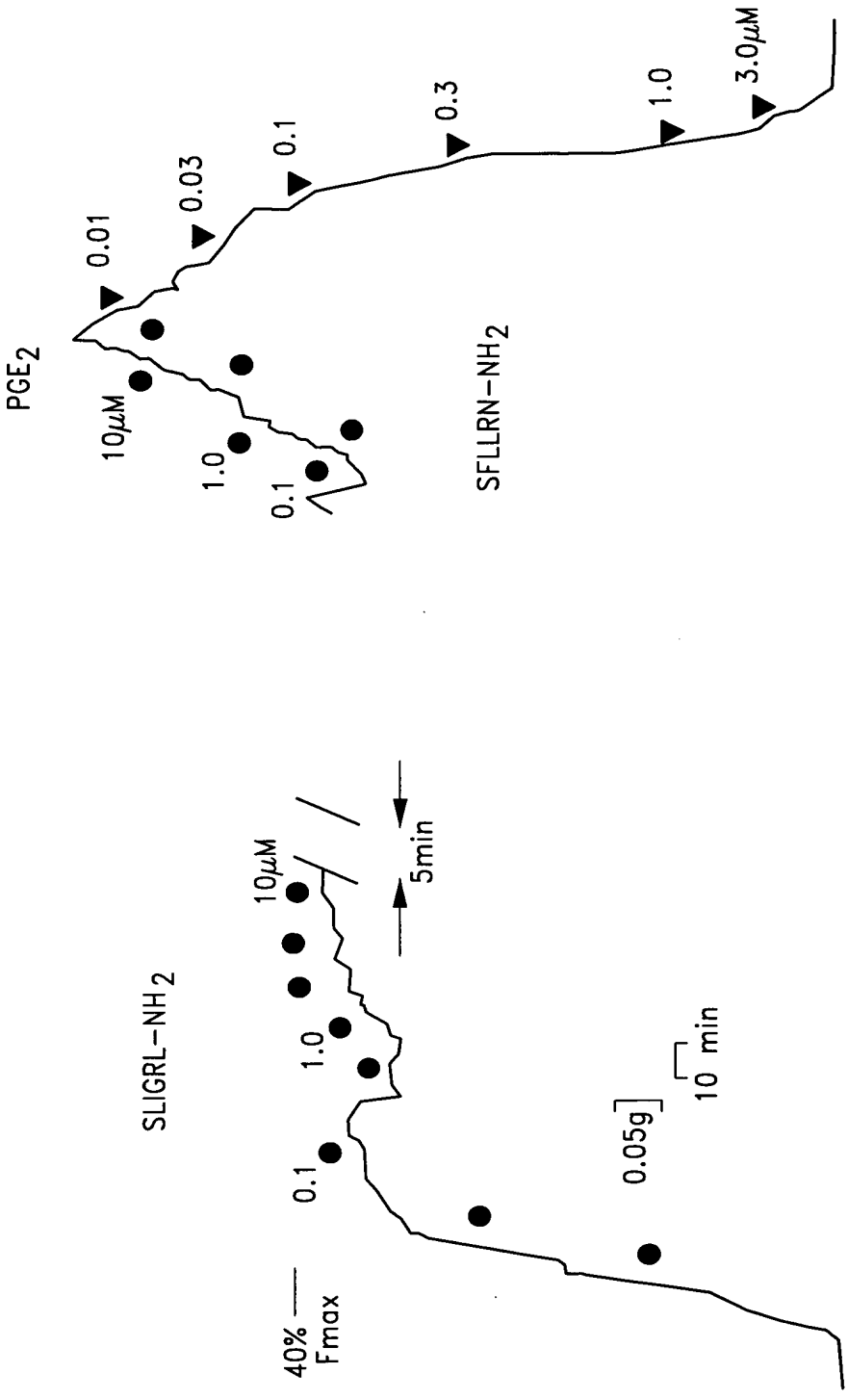

PGE2
10μM
1.0
0.1
0.01
0.03
0.1
0.3
1.0
3.0μM
SFLLRN–NH2
SLIGRL–NH2
10μM
1.0
0.1
40%
Fmax
5min
0.05g
10 min
Carbachol

FIG. 26C

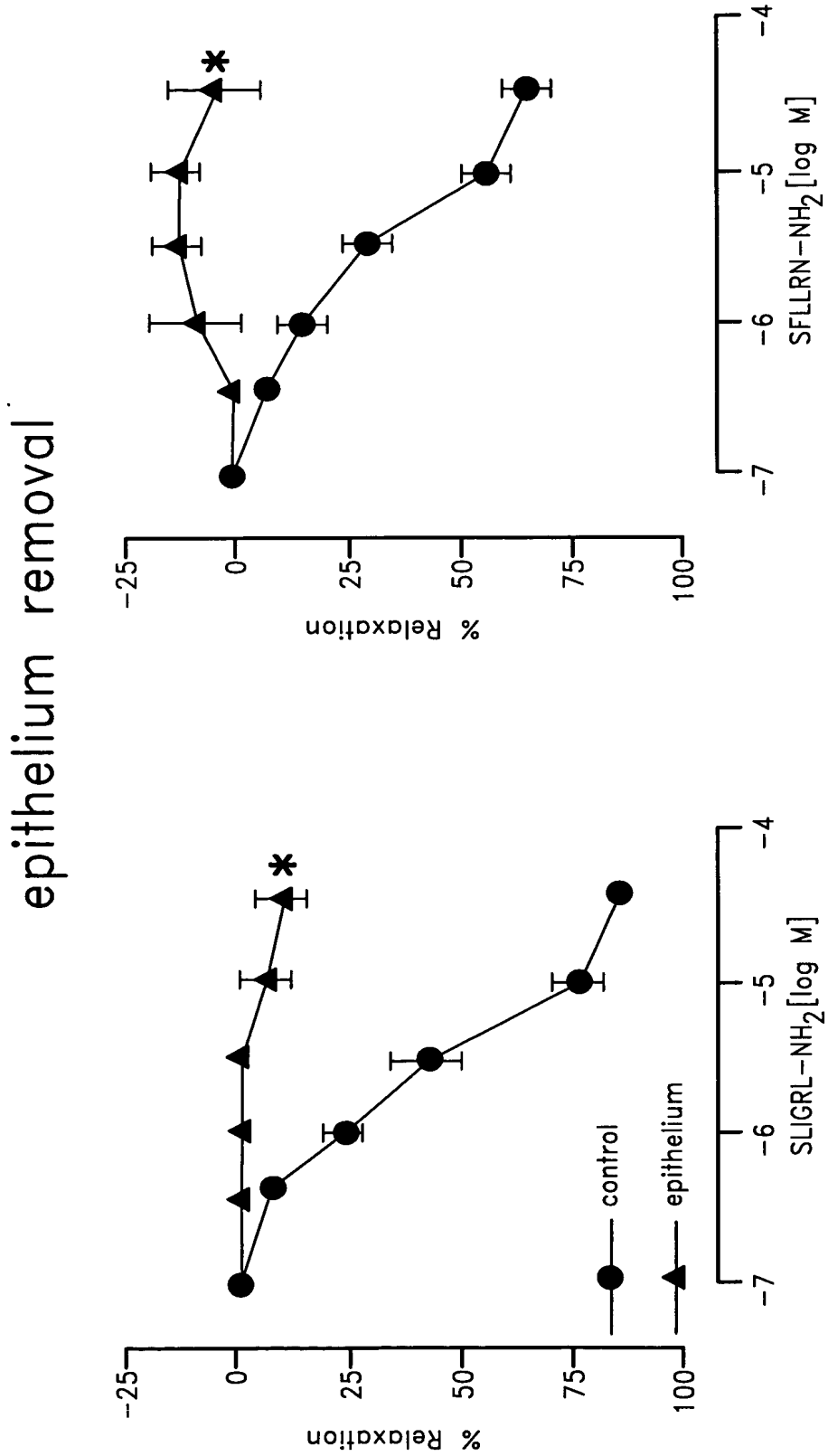

epithelium removal
% Relaxation
-25
0
25
50
75
100
*
control
epithelium
SLIGRL-NH2[log M]
SFLLRN-NH2[log M]
-4
-5
-6
-7

FIG. 27A

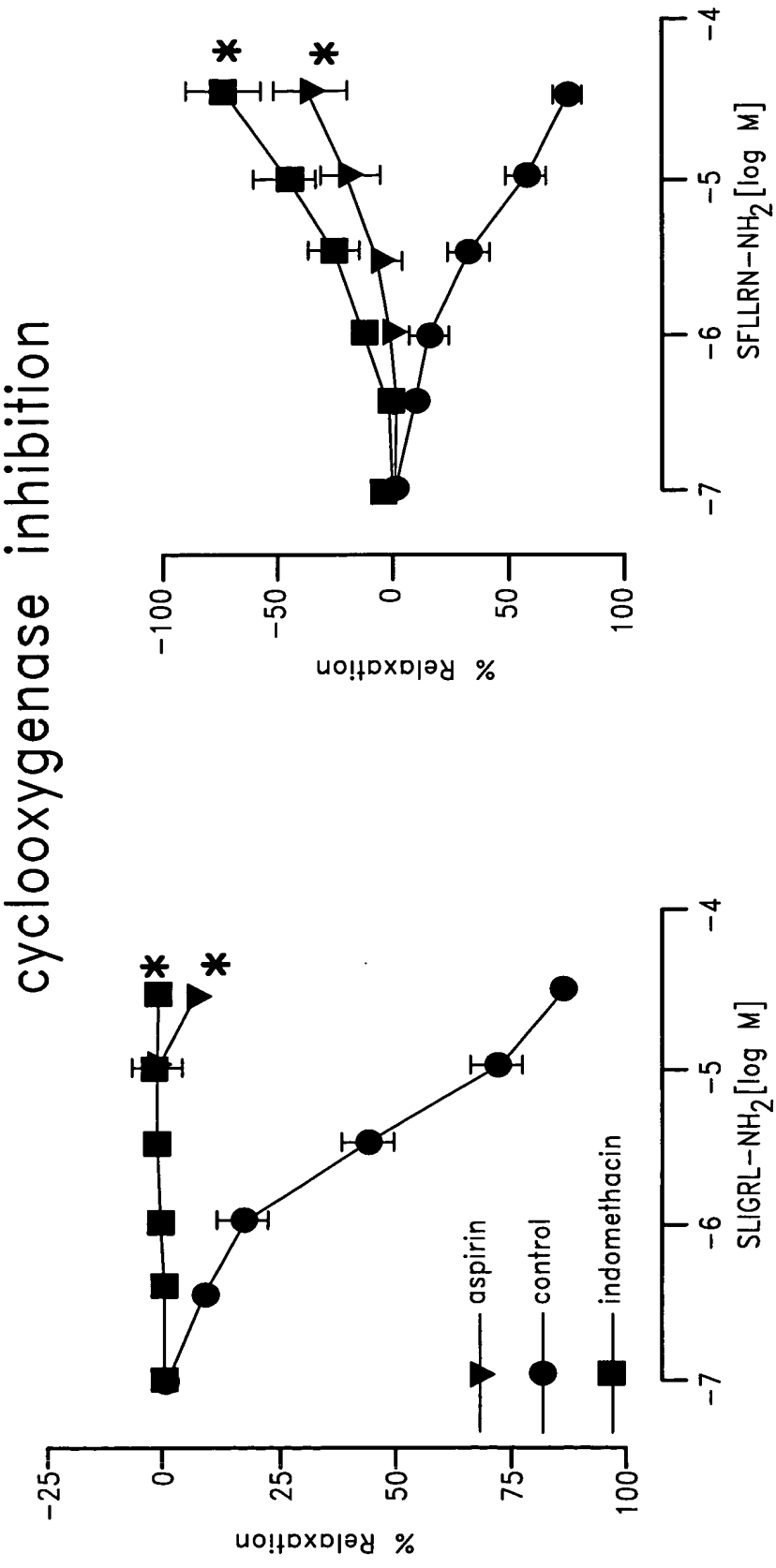

cyclooxygenase inhibition
% Relaxation
-25
0
25
50
75
100
aspirin
control
indomethacin
SLIGRL-NH2[log M]
-7
-6
-5
-4
*
*
% Relaxation
-100
-50
0
50
100
SFLLRN-NH2[log M]
-7
-6
-5
-4
*
*

FIG. 27B

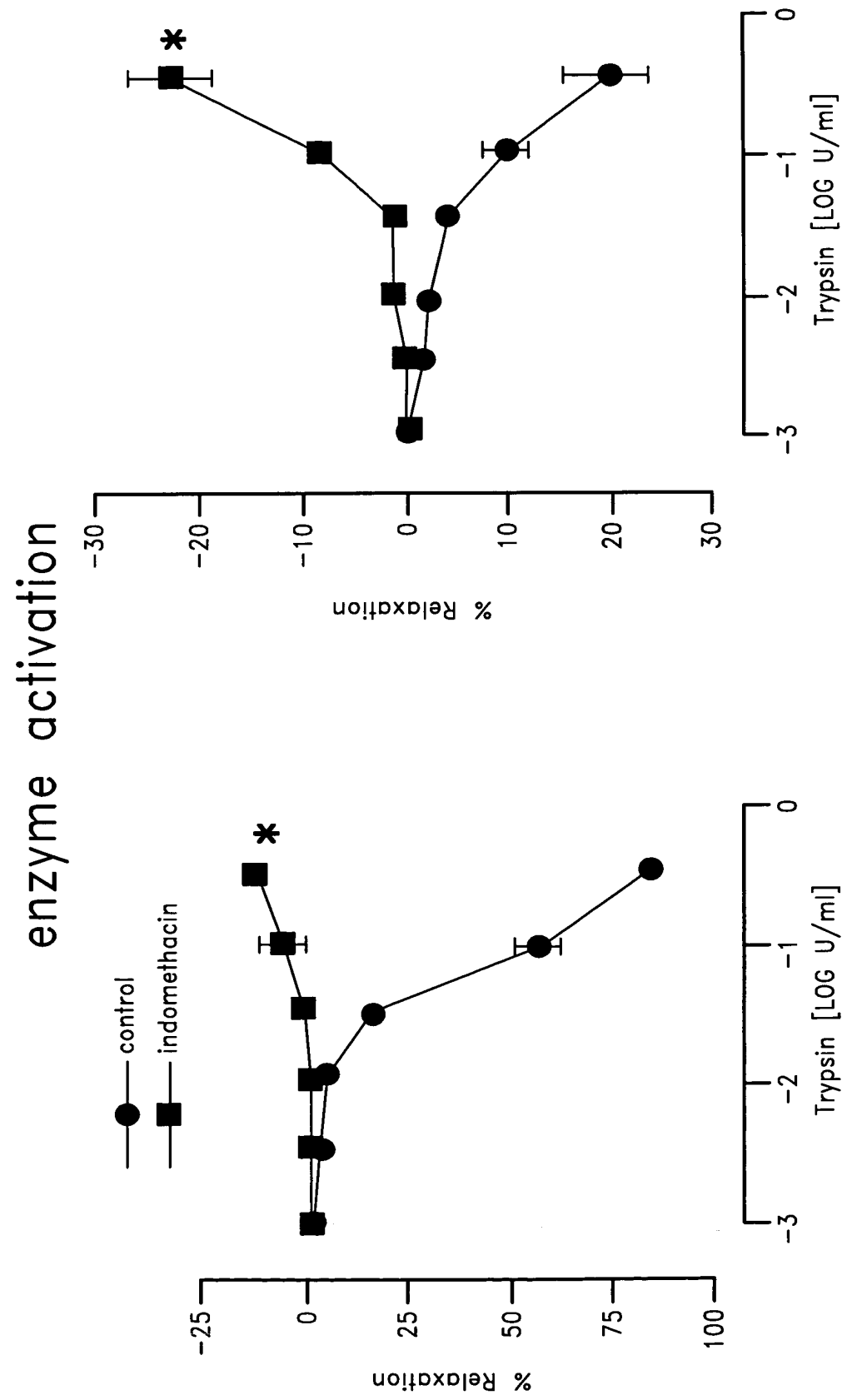

enzyme activation
control
indomethacin
*
*
% Relaxation
-25
0
25
50
75
100
% Relaxation
-30
-20
-10
0
10
20
30
Trypsin [LOG U/ml]
-3
-2
-1
0
Trypsin [LOG U/ml]
-3
-2
-1
0

FIG. 27C

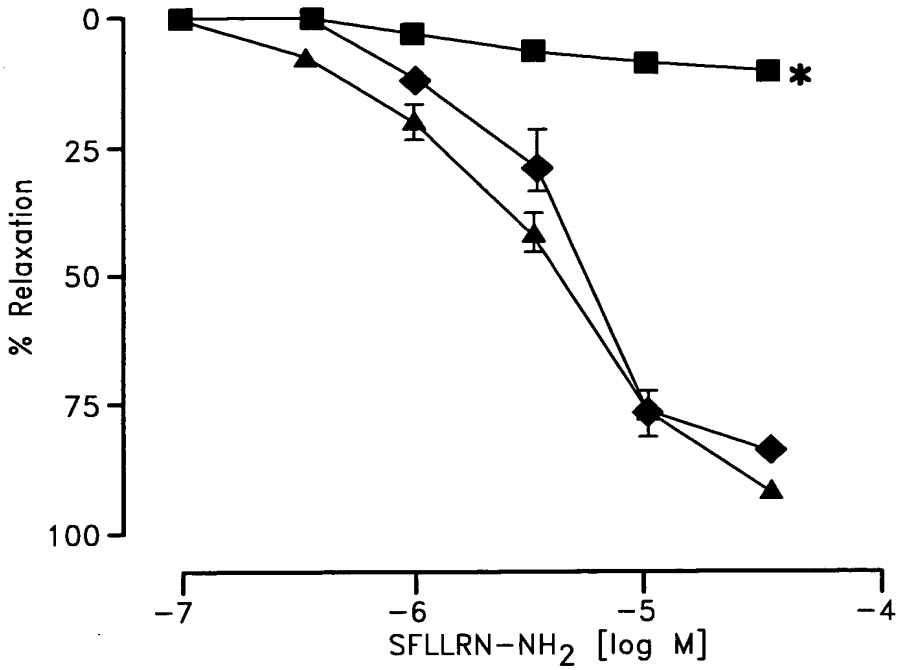


FIG. 28A

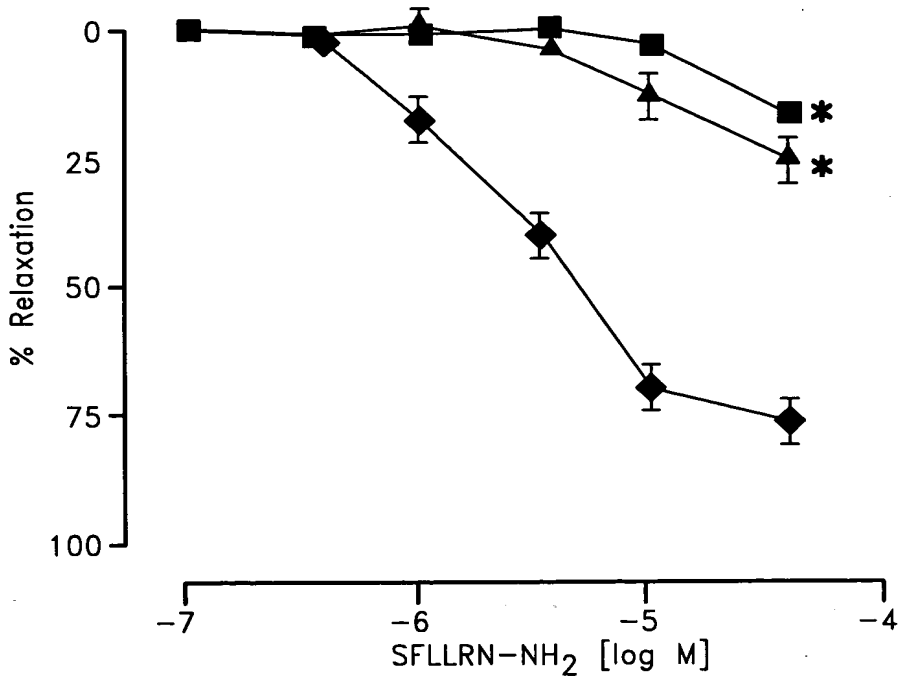


FIG. 28B

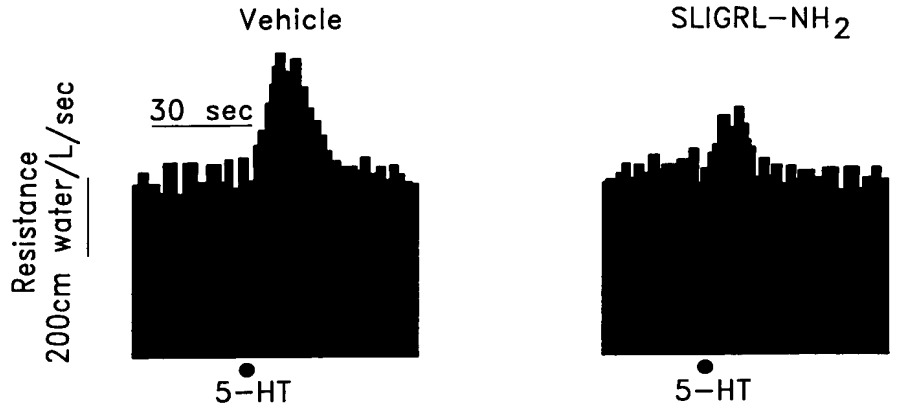


FIG. 29A

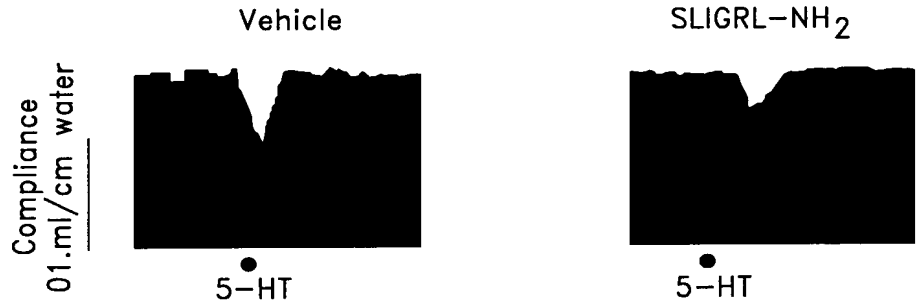


FIG. 29B

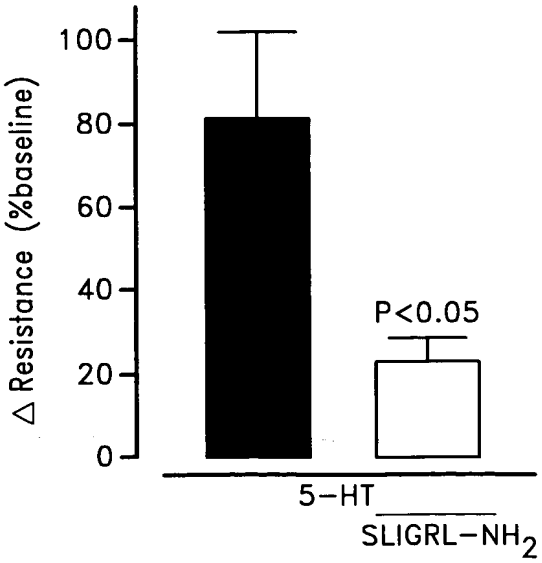


FIG. 29C

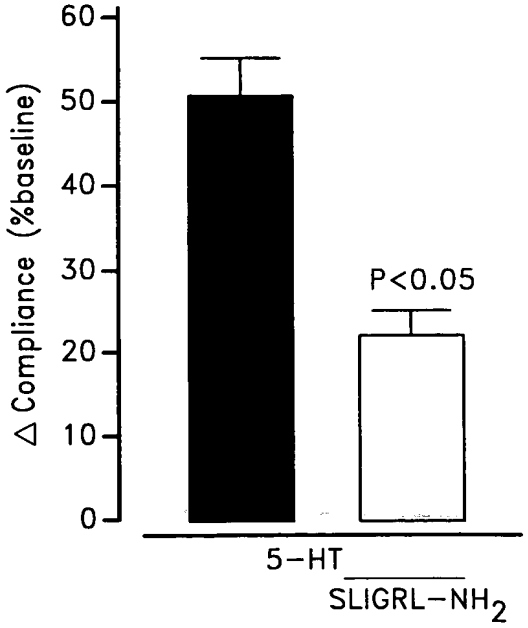


FIG. 29D

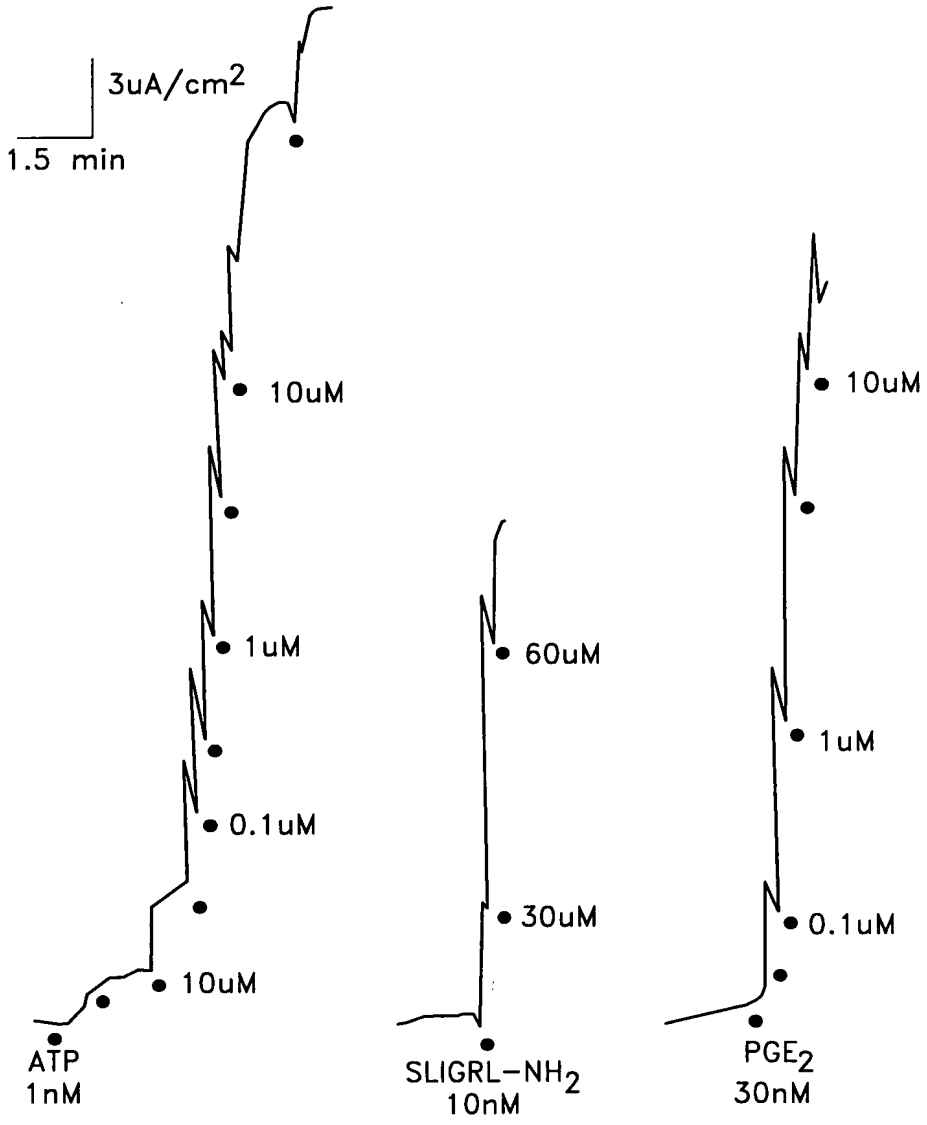

3uA/cm2
1.5 min
10uM
1uM
0.1uM
10uM
ATP
1nM
60uM
30uM
SLIGRL-NH2
10nM
10uM
1uM
0.1uM
PGE2
30nM

FIG. 30

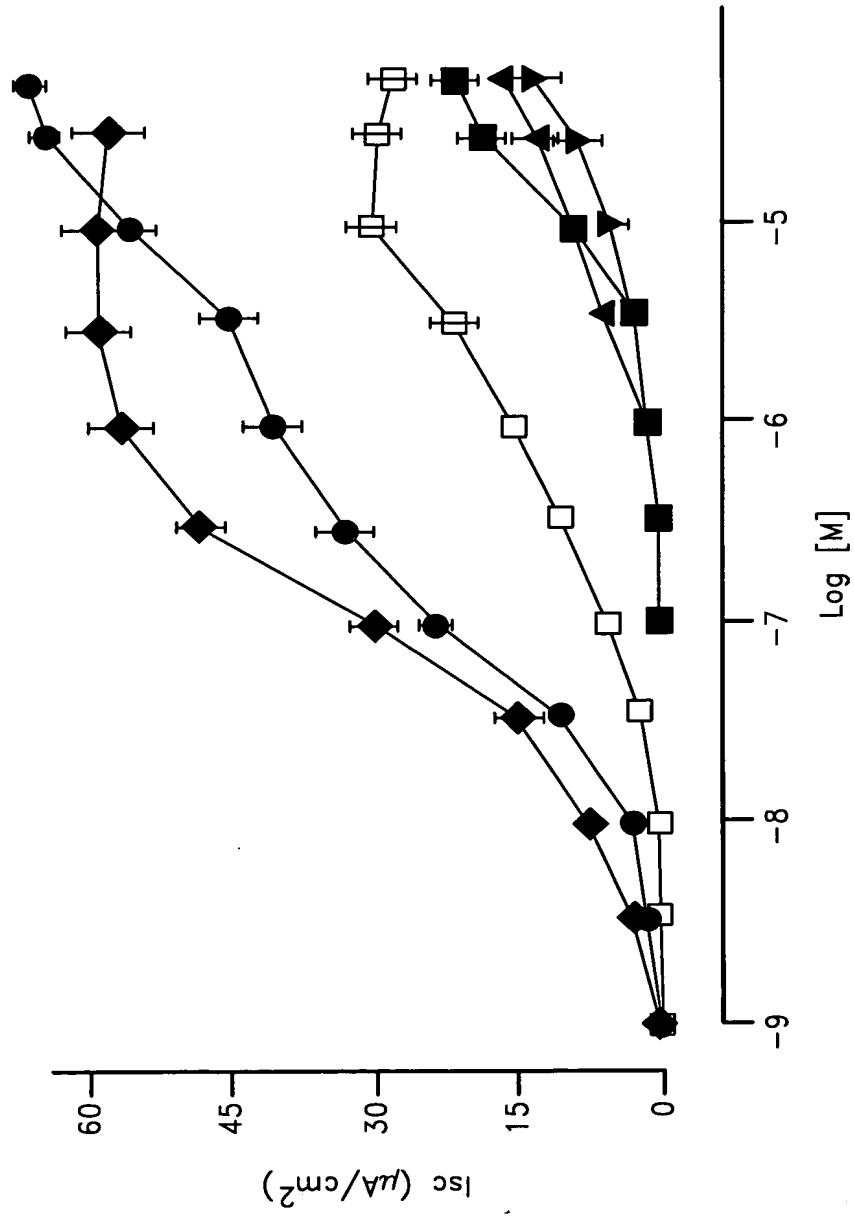


FIG. 31

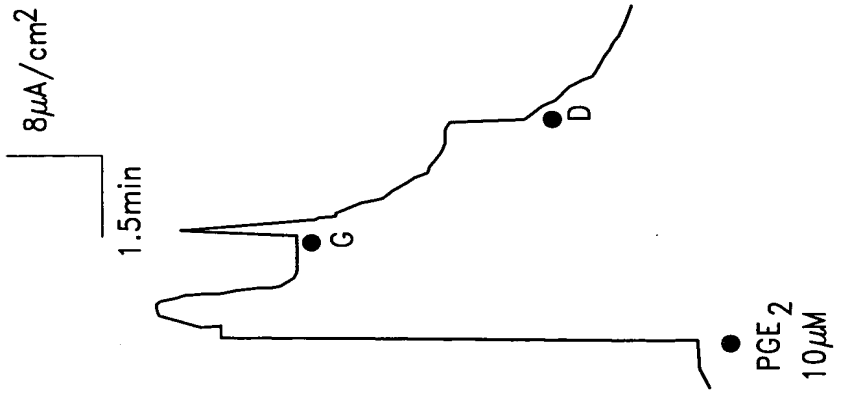


FIG. 32C

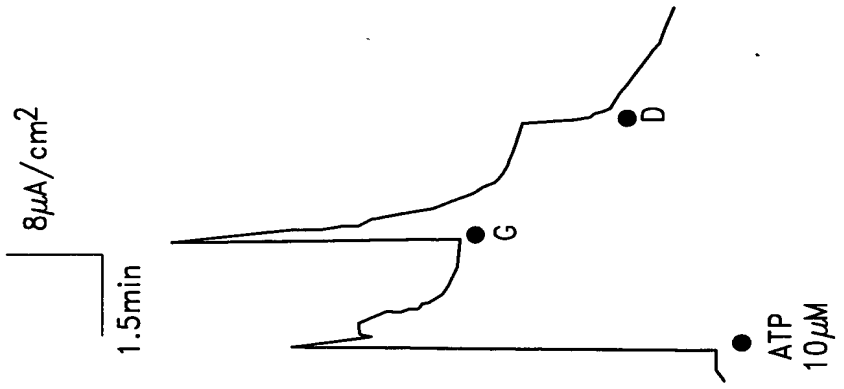


FIG. 32B

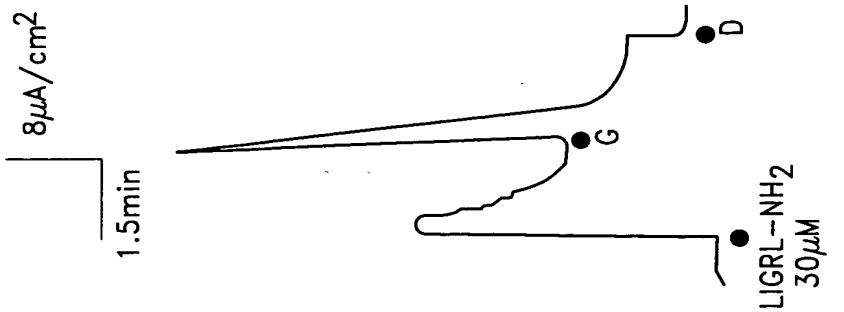


FIG. 32A

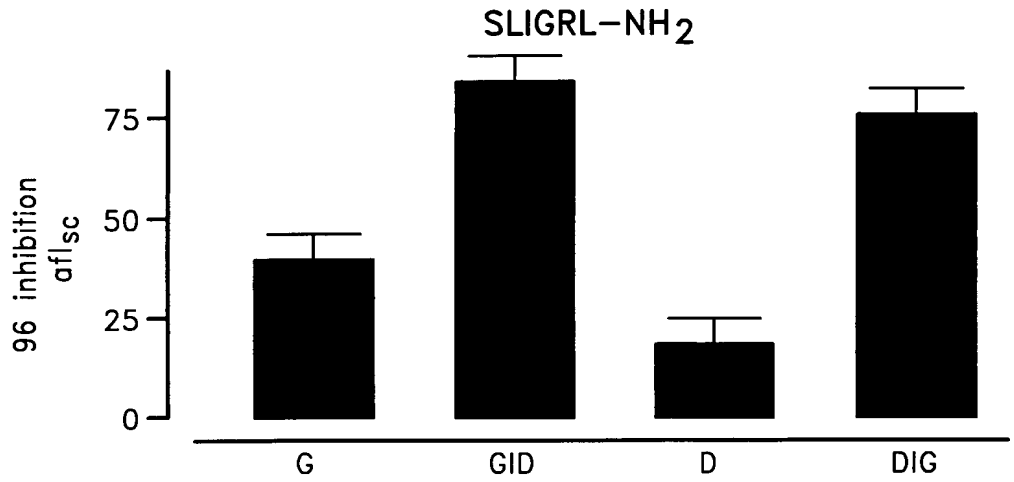


FIG. 33A

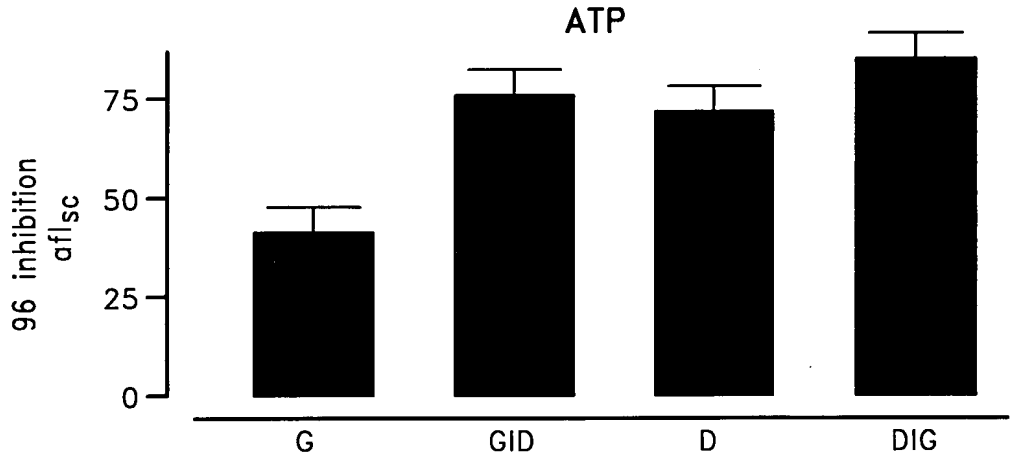


FIG. 33B

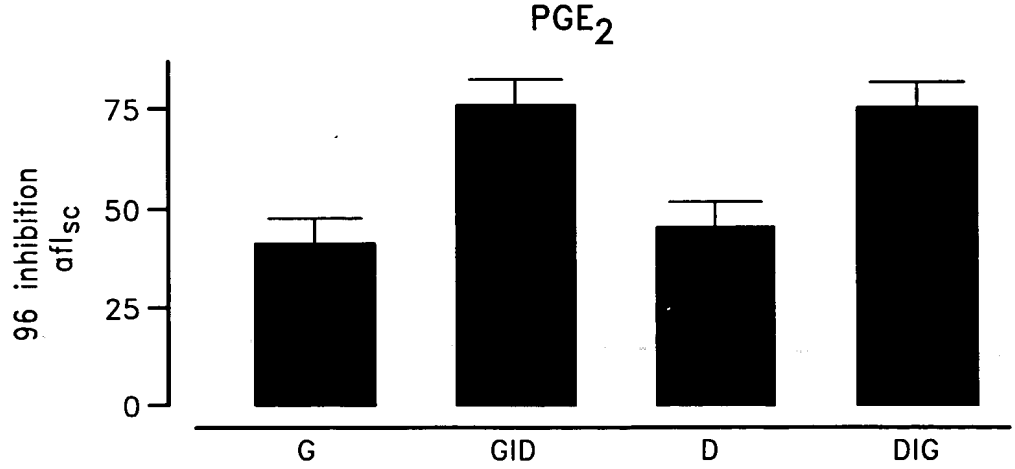


FIG. 33C

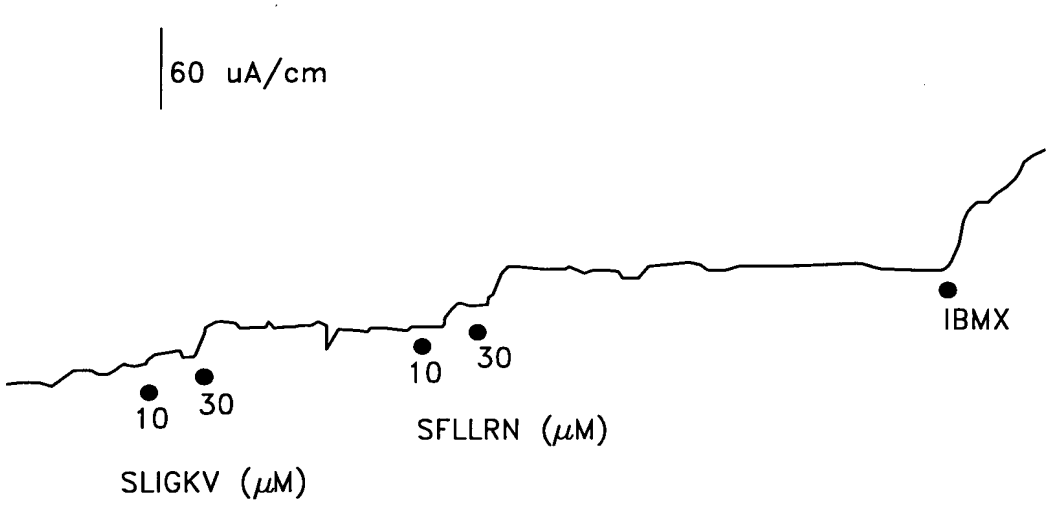

Human Bronchial Epithelium
60 uA/cm
IBMX
10
30
10
30
SFLLRN (μM)
SLIGKV (μM)

FIG. 34

Cytoprotection by epithelium
–derived factors

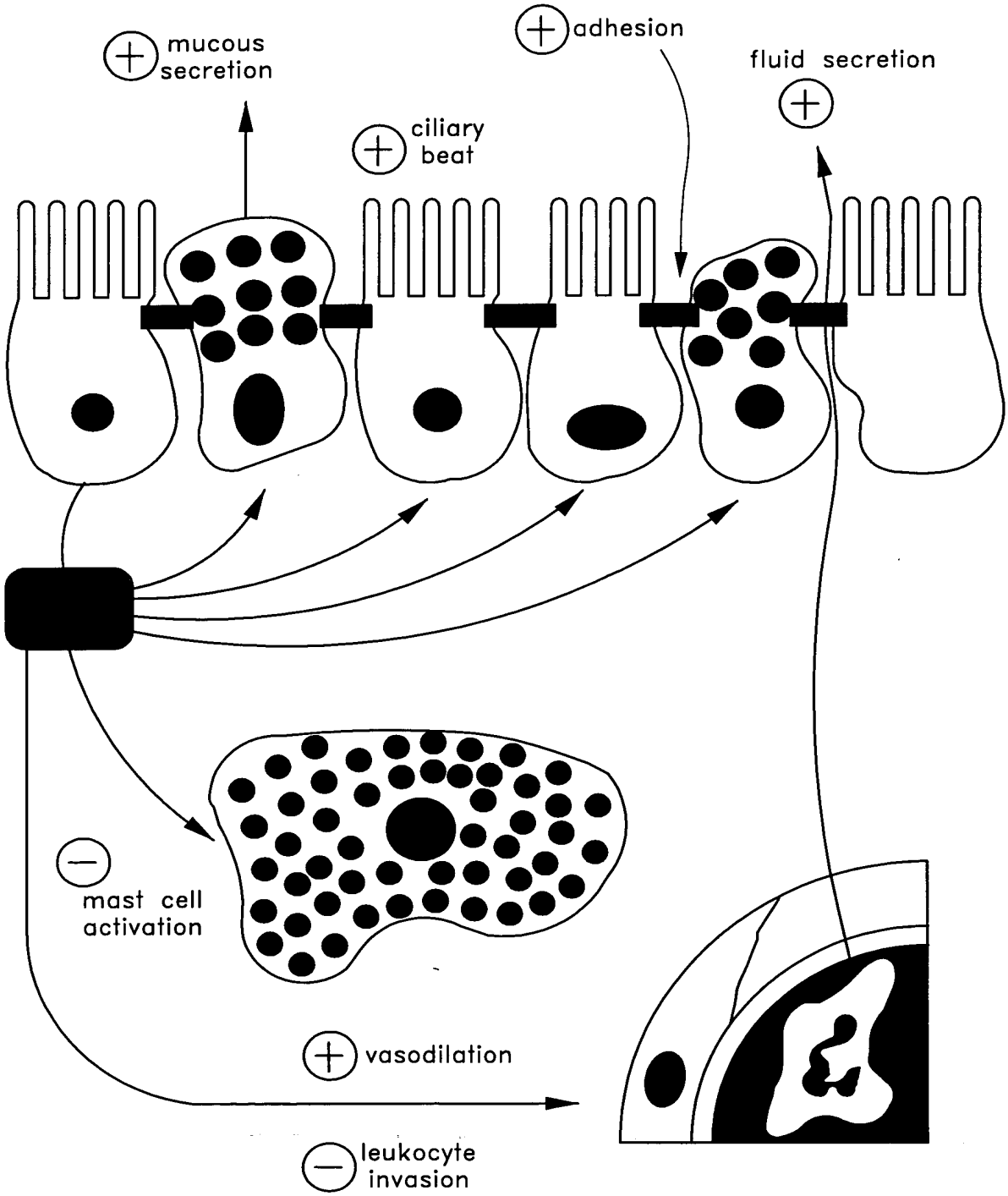


FIG. 35

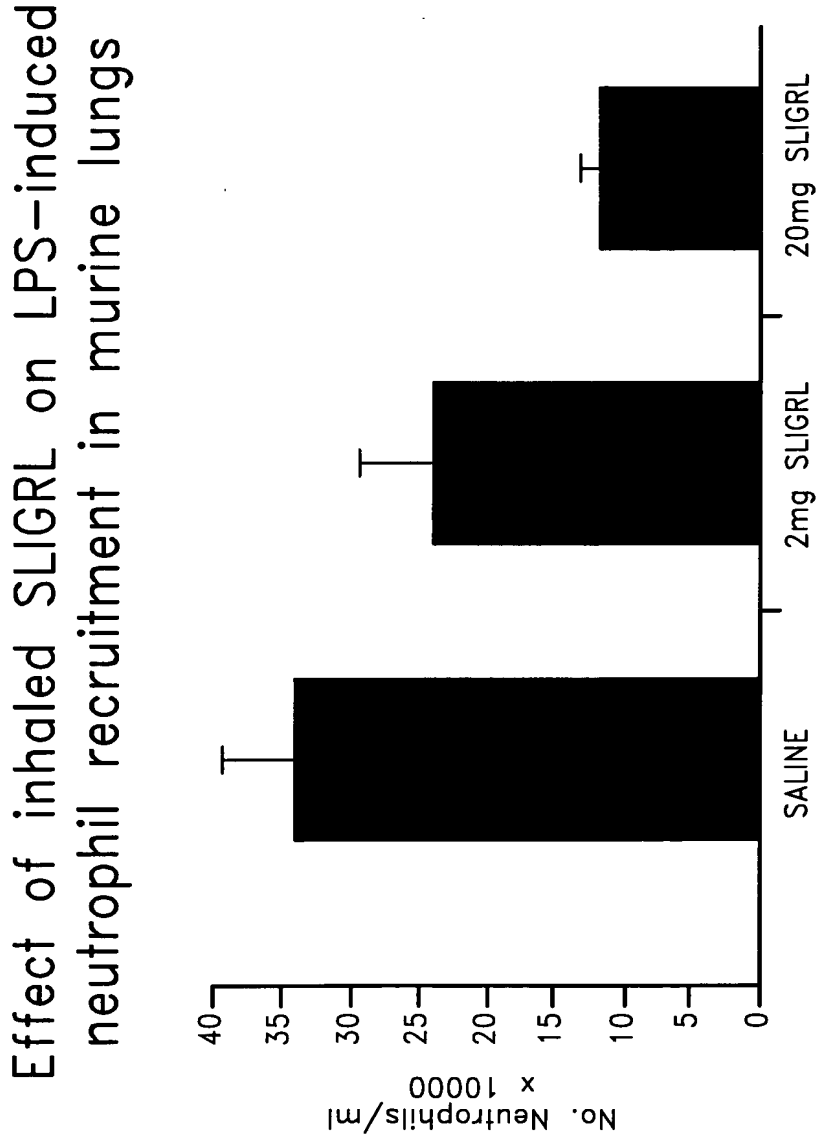

Effect of inhaled SLIGRL on LPS-induced neutrophil recruitment in murine lungs
No. Neutrophils/ml x 10000
40
35
30
25
20
15
10
5
0
SALINE
2mg SLIGRL
20mg SLIGRL

FIG. 36

Monkey Airways

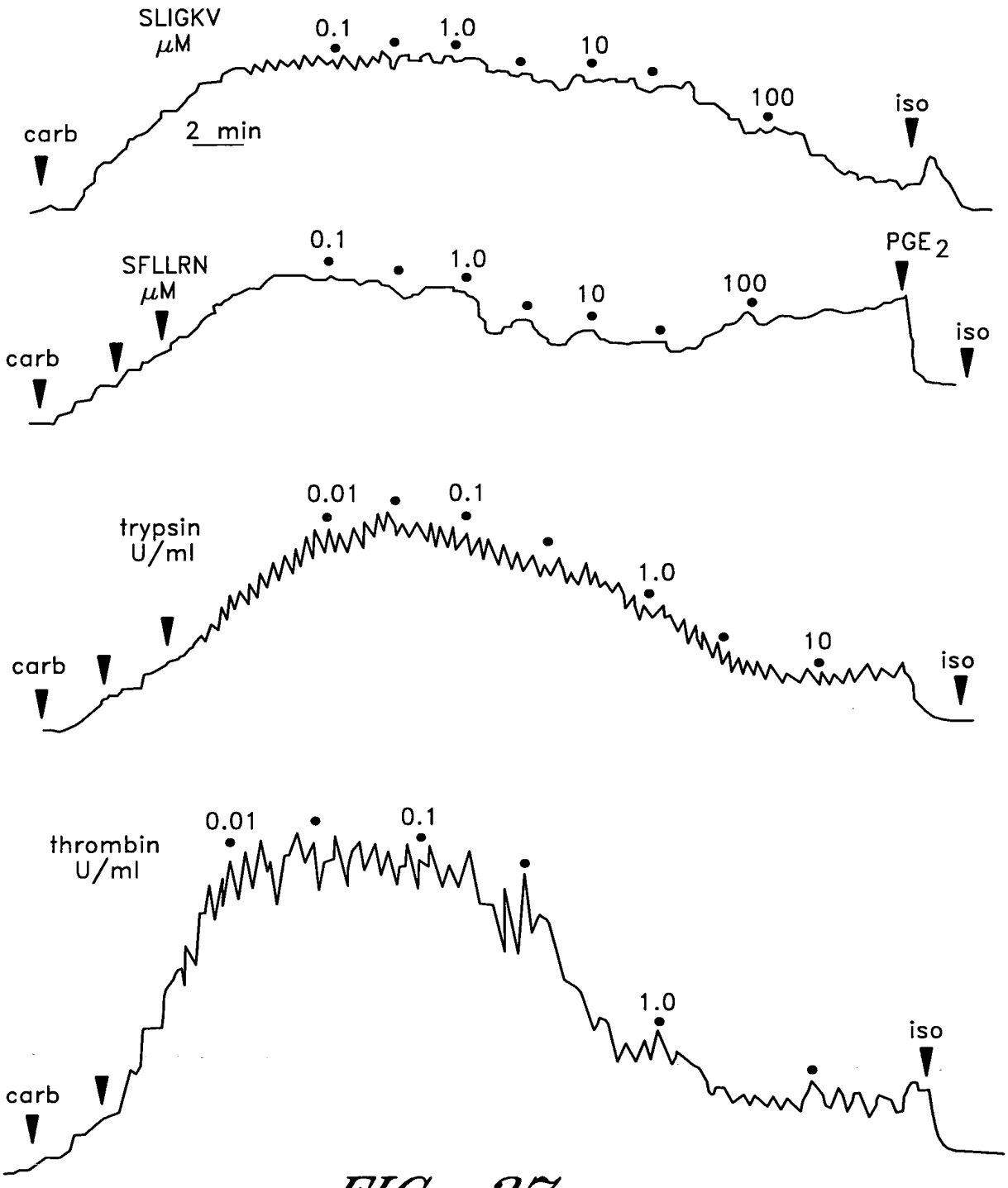


FIG. 37

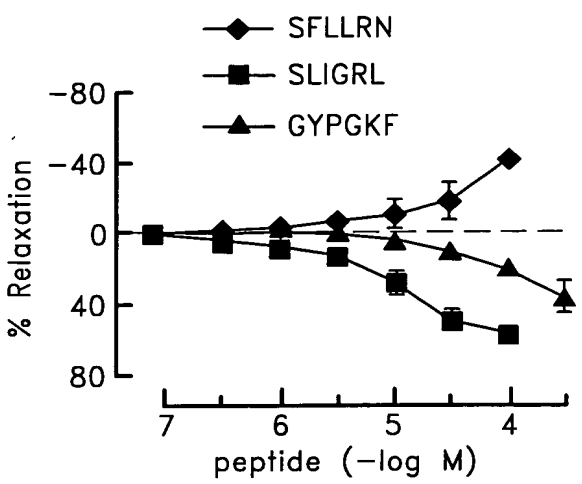


FIG. 38A

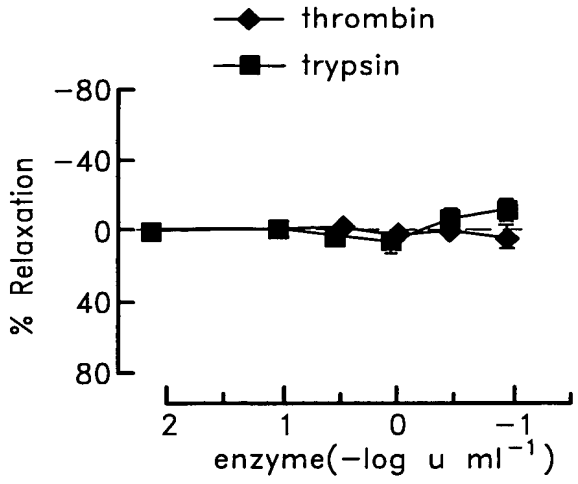


FIG. 38D

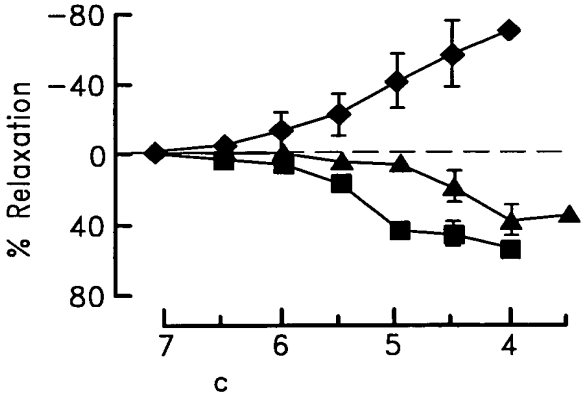


FIG. 38B

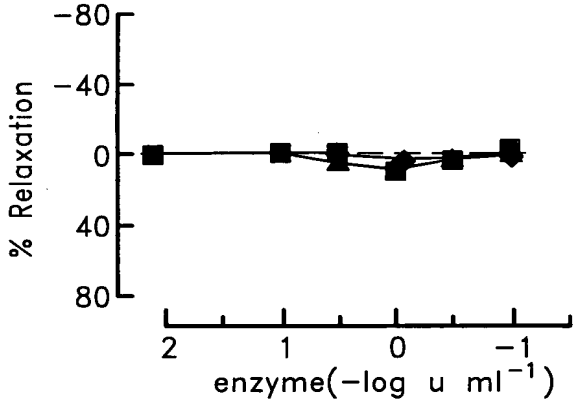


FIG. 38E

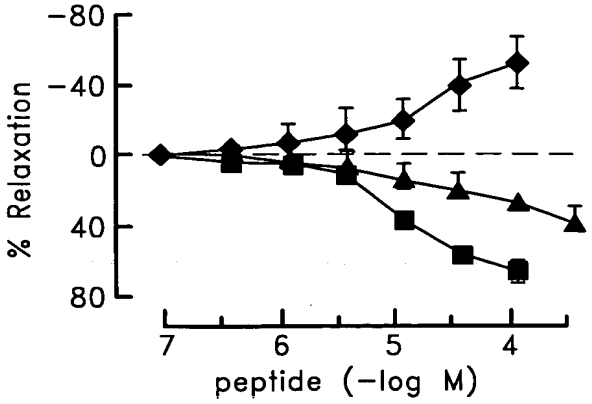


FIG. 38C

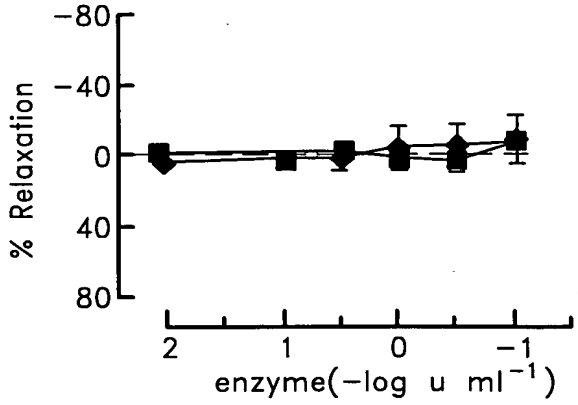


FIG. 38F